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SOME CLINICAL OBSERVATIONS ON AN OUTBREAK OF JAUNDICE FOLLOWING YELLOW FEVER VACCINATION*

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The nature and characteristics of the outbreak of jaundice that occurred in the Army during the Spring and Summer of 1942 has been concisely recorded in Circular Letters No. 45 S.G.O. dated May 13, 1942, and No. 95, S.G.O. dated August 31, 1942. It also received editorial comment in the *Journal of the American Medical Association*.[4]

Of what value then is a report of observations from a General Hospital overseas? Undoubtedly the most interesting and important question is that of etiology, and the nature of the icterogenic agent, a problem for the study of which only limited facilities were available at this hospital. The opportunity, however, of seeing a considerable number of similar cases of jaundice at the same time was unique in the experience of the medical officers concerned, and led to a somewhat different conception of the natural history of the disease, as well as to the recognition of certain symptoms which were unfamiliar. The data on the cases of jaundice observed in the 4th General Hospital is, therefore, recorded for comparison with and inclusion in similar data from other stations. It is apparently very similar to that recently reported from Brazil.[8]

The occurrence of epidemics of jaundice in armies is, of course, well known. Of the American Army, Blumer[2] goes so far as to say that with the possible exception of the Revolution, "whenever troops have been concentrated in this country the disease has usually appeared;" he records outbreaks in the War of 1812, Civil War, and Spanish War, as well as in World War I. In World War I it occurred on the

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Western Front[6] and was common at the Dardanelles.[12] In the present war there was a considerable number of cases among the Australian troops in the Middle East.

Between April 6 and September 30, 1942, 405 cases with jaundice were admitted to this hospital. By May 1, 20 cases had been admitted, and speculation was rife among the officers as to the nature of the epidemic. By the middle of May certain peculiarities in the distribution of cases had strongly suggested the possibility of association with certain lots of yellow fever vaccine. For instance, all of the 13 cases among the officers of the 4th General Hospital were from the group that had been on one transport where they received the vaccine from a single lot, while there were no cases among the enlisted men and officers who were on another transport and were vaccinated from a different lot. All the officers had been living in intimate contact both before embarking and after debarking the latter part of February. That jaundice had followed the use of certain yellow fever vaccines was also known from Findlay's reports.[7]

Of the 405 cases, the records of 398 were suitable for study. In 183 cases the date of yellow fever vaccination was known. The mean interval between vaccination and appearance of jaundice was 100.1 days; the shortest interval 66 days, and the longest 210 days. The median was 94 days. In only 28 (15%) of the cases was the interval greater than 120 days. These men were recorded as having been vaccinated from 16 different lots, but in only 4 was there a sufficient number to compare the interval between vaccinations and jaundice with different lots of vaccine. There was no significant difference. Seven patients gave a history of having had "catarrhal jaundice" from 6 months to 20 years previously. One patient stated that he had received yellow fever vaccine in October, 1939, before going to South America for an oil company and that he developed jaundice in January, 1940, together with a number of other employees of the same company. It was not possible to confirm these statements.

TABLE 1.—INCIDENCE OF PRESENTING COMPLAINTS IN 398 CASES

Jaundice	273	Weakness	28
Anorexia	63	Vomiting	23
Nausea	63	Malaise	6
Epigastric distress	56	Hives	2

The symptoms and mode of onset were almost indistinguishable from the "infectious hepatitis" described by Findlay,[6] Blumer,[2] Norton,[13] Pickles[4] and others. The onset was usually insidious, with anorexia, epigastric discomfort and dark urine. In many cases, however, the discoloration of skin and sclera was the first abnormality noted, and other symptoms did not develop for several days after icterus was apparent. The early appearance of dark urine is quite constant and usually noticed by the patient and is extremely valuable in early diagnosis. The more common presenting complaints are listed in Table 1—the total exceeding the number of patients for obvious reasons. The incidence of these and of certain other common symp-

toms is shown in Table 2. Urticaria occurred in only 10 patients, but was the presenting complaint in 2. The urticaria preceded the jaundice by 1 to 13 days, usually 7, and consisted of a few large wheals more commonly on the trunk than extremities. One patient developed urticaria after 22 days of jaundice.

TABLE 2.—INCIDENCE OF PRINCIPAL SYMPTOMS IN 398 CASES

	No.	%		No.	%
Jaundice	398	100.0	Diarrhea	46	11.5
Anorexia	316	79.3	Malaise	40	10.1
Nausea	257	64.5	Fever	64	16.1
Epigastric discomfort	185	46.2	Pyrosis	60	15.1
Weakness	202	50.7	Sleepiness	21	5.3
Vomiting	135	33.9	Upper resp. symptoms	35	8.7
Eructations	108	27.1	R.U.Q. pain	26	6.5
Headache	79	19.8	Urticaria	10	2.5
Constipation	82	20.6			

It was difficult to obtain sufficiently accurate histories from many patients to determine the relation between the time of onset of symptoms and the appearance of jaundice. Ten patients gave a definite story of anorexia for between 2 and 4 weeks before the onset of jaundice, whereas 6 maintained that they had had epigastric or right upper quadrant pain for the same interval. An attempt to show the relation between the onset of symptoms and the appearance of jaundice is presented in Table 3. The apparent onset of symptoms and jaundice

TABLE 3.—RELATION OF ONSET OF SYMPTOMS TO APPEARANCE OF JAUNDICE

Days Before jaundice	Anorexia	Epigastric pain	Nausea	Dark urine	Any symptoms at all
14	5	2	5	3	13
13	3	3	2	4	16
12	1	2	..	3	11
11	2	1	1	1	8
10	6	3	3	4	19
9	2	1	4	2	13
8	6	2	7	7	29
7	**28**	15	**21**	28	96
6	8	5	5	15	42
5	10	7	7	25	61
4	15	**16**	9	14	63
3	18	8	14	**42**	98
2	18	6	13	28	76
1	6	2	4	30	53
0	27	13	20	**77**	148
After jaundice					
1	2		1	4	
2	2	..	1	2	
3	1	2	2	2	
4	1	1			

at the same time is due to the large number of mild cases whose first knowledge that they were not well was when some friend told them that they were yellow. In the more typical and severer cases there were definite symptoms for a week before jaundice was detectable. The incidence of upper respiratory symptoms at the onset was considerably less than is usually encountered in epidemics of infectious hepatitis. Some 21 patients complained of unusual drowsiness and,

among these, this was a striking symptom. They slept almost continuously for several days, although could be aroused readily and when awake were completely clear.

The liver was recorded as palpably enlarged in 285 cases (71.6%). This is considerably higher than the figure of 20% given in Circular Letter No. 95. In 209 of these patients there was complaint of pain or tenderness on palpation of the liver, while in 76 instances the enlarged liver was not painful. Forty additional patients in whom the liver could not be felt complained of pain or tenderness in the right upper quadrant. The enlargement of the liver was usually only moderate, in only 21 cases was it recorded as being more than 5 cm. below the costal border. The spleen was palpable in 26 patients, and was usually not tender. A temperature above 99° F. during the period of hospitalization was recorded in only 68 (17%) of the cases. In 44 of these the maximum was below 100°, in 15 between 100° and 101°, and in 2, 104° F. The fever rarely lasted more than 2 or 3 days. A very few ran an irregular fever for a week to 10 days; a similar small group complained of frank chills. While on the wards a number of observers had commented on slow pulse rates, the bradycardia frequently associated with jaundice was not borne out by a study of the records. During the first 3 days of hospitalization only 1 patient had a mean resting heart rate below 50 per minute; in 13 it was between 50 and 60; in 98 between 60 and 70; and in 196 between 70 and 80. Seventy-nine had a mean resting heart rate between 80 and 90 per minute; 4 between 90 and 100, and only 1 over 100 beats per minute. This is a normal distribution.

Aside from the vague discomfort associated with the general feeling of malaise, severe joint or arthritic pains were distinctly uncommon, being recorded in only 2 instances.

In addition to the urticaria mentioned as one of the early symptoms, various skin eruptions occurred during the course of the disease. These included erythema, maculo-papular eruptions lasting a few days, usually over the trunk, petechia, purpura, and bleeding gums. Two patients had melena, 1 had an attack of erythema nodosum at the height of the jaundice. Two patients bled profusely enough to require transfusion, 1 from the bowel, and 1 from the gums. The tourniquet test was negative in all. Unfortunately at the time it was not possible to carry out prothrombin determinations.

One of the most striking phenomena, usually in the more severe and protracted cases, was the development of typical spider telangiectases, with a small central arteriole, pin-point pressure on which would cause the whole nevus to blanch. These occurred on the face, but were more common over the shoulders and pectoral regions. During recovery they completely disappeared and could not be seen or demonstrated, even when a particular lesion had been ringed for accurate localization.

Icteric indices were estimated on 337 patients. Usually one determination was made on admission, and subsequently at intervals if the jaundice seemed to be deepening. The mean of the maximum

icteric indices recorded for each of these patients was 64.4, the greatest number (55) being between 40 and 49. The distribution is shown in Table 4. Of the 16 patients with icteric indices over 150, 6 (37.5%) were over 30 years of age, while 22.3% of the whole group were over 30.

TABLE 4.—MAXIMUM ICTERIC INDEX

Icteric index	No. cases	Icteric index	No. cases
<10	1	80–89	15
10–19	19	90–100	13
20–29	38	100–109	13
30–39	45	110–119	11
40–49	**55**	120–129	14
50–59	29	130–139	7
60–69	32	140–149	5
70–79	28	>150	16

The difference is too slight to constitute evidence of a greater severity of the disease in the older group. In a small group icteric indices were determined at approximately weekly intervals. A chart of the results on 5 of these patients is shown in Figure 1. It is apparent that after

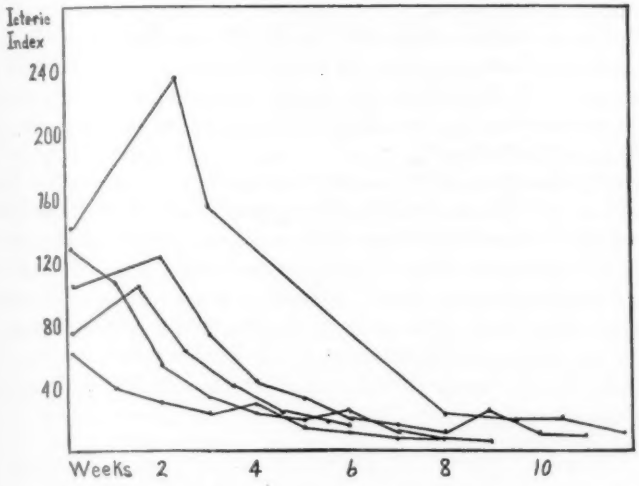

FIG. 1.—Rate of fall of icteric index.

convalescence begins, the chromogenic material in the serum diminishes at a more rapid rate during the first few weeks than it does later, although at this time the liver might be supposed to have recovered more fully. The reason for this is not clear. Attempts to estimate the icteric index from the color of the skin and conjunctiva during convalescence had a high error. It may be an expression of the relative amounts of bilirubin free in plasma and bound to plasma protein, or possibly some of the pigment is more firmly fixed in the tissues than the rest. It should be pointed out, however, that a similar type of curve of the elevation of bilirubin is obtained after its intravenous injection in normal individuals. After injection of sufficient bilirubin to raise the plasma concentration to 4 to 8 mg per 100 cc. (icteric

index 60 to 100), the blood level will have returned to normal in about 24 hours and none appears in the urine, the blood level falling along an exponential curve.

The urine was examined during the height of the disease in 329 patients. Sixty-one (18.5%) of these showed albumin; in 41 a trace, 15, 2+, and 4 a cloud. In all who recovered, the albumin disappeared before discharge. Abnormal numbers of cells or casts were not encountered. In no urine tested could a positive test for bile salts be obtained with either Hay's or Pettenkofer's test, although the specimens contained large amounts of pigment. In the severer cases there was a definite tendency for the specific gravity to be low, even when the volume was small, as in other types of so-called "bile nephrosis."

The onset of convalescence was not infrequently heralded by a profuse diuresis which persisted for several days and was not due to any significant increase in fluid intake. This aroused interest and speculation, but facilities were not available for study of its mechanism. It is recorded in the hope that it may be investigated when and where opportunities occur.

The infrequency of itching was a striking finding. Even the deeply jaundiced patient rarely complained of it, even on direct questioning. It was recorded as being present in only 13 patients. This, with the apparent absence of bile salts in the urine, invites speculation. Unfortunately, facilities were not available for estimation of the concentration of bile salts in the blood.

The mean leukocyte count in 194 examinations was 7620. There were only 15 counts above 10,000, the highest being 14,600, the lowest count was 4000. A careful differential count was made in 47 cases by an officer with special training in hematology (see Table 5). The commonly reported lymphocytosis in "catarrhal jaundice" was not found in these cases. The leukocyte count and differential must be regarded as within normal limits, and therefore, not of diagnostic value. Nor could any significant change in the smear be detected during the course of the disease.

TABLE 5.—DIFFERENTIAL LEUKOCYTE COUNT IN 47 CASES

	Average	Maximum	Minimum
Neutrophils	58.2	79.0	32.0
Lymphocytes	29.6	59.5	10.5
Young lymphocytes	2.2	15.0	0.0
Mononuclears	6.7	16.0	0.0
Eosinophils	2.3	5.5	0.0
Basophils	0.9	3.0	0.0

The mean sedimentation rate (Wintrobe method) in 215 cases was 11.6 mm. per hour. In only 39 was it above 15 mm. per hour. There was no relation between the intensity of jaundice and the more rapid sedimentation rates. The sedimentation rate was considered to be unaffected by this disease, the rapid rates observed being due to coincident upper respiratory infections.

The stools were rarely acholic, although an abnormally light color for a few days at the height of the disease was common. In only 85

cases, however, was this sufficiently noticeable to be recorded on the charts, and in only 10 cases are the stools recorded as "acholic" or "clay-colored." Unfortunately, at the time, the chemical tests were unreliable.

The cephalin-cholesterol flocculation test[10] was performed on 220 cases. On many of these it was repeated weekly until the test became negative. This test was selected in preference to other liver function tests for the following reasons: It is relatively easy to perform on large groups of patients; it is not invalidated by the presence of jaundice or disturbances in kidney function; and is primarily intended to show the presence of active parenchymal disease in the liver. Since one of the most important problems was to determine when a man should return to duty, this last feature was regarded as of importance. The technique was carried out exactly as originally described, but at first controls would be positive and all results had to be discarded. It was found out more or less by accident that it was first necessary for cephalin to "age" or oxidize for from 3 to 6 weeks. When solutions were made from the older cephalin, no more false positives occurred. We later found this had been noted by Rosenberg.[15] Opportunity to control the specificity of the test has been limited to 5 cases. These all showed negative reactions and were proved at operation to have obstructive jaundice, in 2 cases from stone and in 3 from carcinoma. The test is also positive in infectious mononucleosis as noted by Hanger, and it has recently been found to be positive during the acute phase of malarial fever. In all the early cases with acute symptoms the test was positive. In the average case the test would become negative in 3 to 4 weeks. This was usually by gradual change from 4+ to 2+ or down to negative, but a small group went from strongly positive to negative in a period of 1 week. It was quite usual for the test to become negative before signs of clinical jaundice disappeared. The converse was also true; a few cases were followed where jaundice had disappeared and the flocculation persisted. Most of these patients continued to complain of malaise and right upper quadrant pain on exertion. In 18 cases tests were done at weekly intervals for from 2 to $4\frac{1}{2}$ months before the result was negative. These serial tests showed that, in spite of negative controls, the sensitivity of the reaction would occasionally vary from week to week. This was evident when three-quarters of the group would have a stronger reaction than the previous week, though their clinical condition was unchanged or improved.

From clinical observations it is felt that the flocculation test is of value in determining when the period of active liver damage is ended and in selecting those cases in which a prolonged period of convalescence is indicated.

Tests for urobilin in the urine were performed on 45 cases. Schlesinger's method was used and tests were repeated at intervals of 3 days. It was found that random single specimens were of little value, as false positives were frequent. This was corrected by using only samples from the total 24 hour urine volume. This intermittent excretion rate of urobilinogen in the urine has been fully described by Watson. It

was found that urobilinogen was usually absent from the urine during the acute phase with rising icterus, even when duodenal drainage showed some bile present in the intestinal tract.

During the early stage of recovery, tests for urobilin were very strongly positive, and then graded off to negative as the hyperbilirubinemia receded. The cephalin-cholesterol flocculation test became negative before urobilinogen disappeared from the urine on serial examinations. In 8 cases, urobilinuria cleared with recovery for from 7 to 14 days, then recurred and persisted for from 10 days to 2 weeks, without apparent change in the patient's condition. We have no explanation for this.

Duodenal intubation was carried out in 50 cases in all stages of the disease. In the first 20 cases the position of the tube was checked fluoroscopically; thereafter when a free flow of bile-stained fluid was not obtained. A sample (A) was collected, and then 50 cc. of warm 25% magnesium sulfate introduced. Ten minutes later a second specimen (B) of 50 to 75 cc. was taken and separated from a third (C) specimen. Microscopic examination was done on the B and C specimens. Free HCl was present in the stomach of all but 2 cases, a normal finding. Bile was always present in the duodenal contents, even when the jaundice was severe and mounting. However, the specimens were usually cloudy and very viscid, even allowing for contamination by gastric contents. Stimulation by magnesium sulfate in no case caused a flow of dark brown gall bladder bile. This was true even in cases where the patient had recovered clinically and jaundice had nearly cleared. Apparently the gall bladder is in a state of stasis for several weeks, even in mild cases.

On direct microscopic examination of the centrifuged duodenal sediment of the B and C specimens, some of the cases showed a moderate to marked cellular exudate. Many of these cells appeared to be neutrophilic leukocytes. Better to determine their nature, the duodenal contents were directly aspirated into formalin and fairly satisfactory hematoxylin and eosin stains prepared. It was then seen that the cells, apparently leukocytes, were in reality mononuclear cells with fragmented nuclei. The cells appeared definitely abnormal, the most striking change being the fragmentation, pyknosis and karyorrhexis of the nuclei. In addition, vacuoles in the cytoplasm were frequently noted. It was thought that these cells were associated with the disease in the liver. Slides were made from 17 cases of hepatitis and 10 with no evidence of liver disease. In 7 of the 17 cases of hepatitis, and in 3 of the control series, the abnormal cells previously described were found. In reviewing the experiences of others in duodenal intubation, it was found that Fidler, Innes and Davidson[5] had presented good evidence that these cells were due to the local irritation of the magnesium sulfate. The cells they found following its use were identical with ours, and they, too, at first identified them as leukocytes. It seems important to emphasize that, in studying the cellular content of duodenal and biliary secretions, concentrated magnesium sulfate should not be used as a stimulant.

Attempts were made to isolate a possible etiologic agent with the material available. These were uniformly negative, and are recorded merely as a matter of record. Duodenal contents from 5 patients were collected shortly after jaundice developed, pooled, filtered through Elford membrane with a pore diameter of 600 μm. The sterile filtrate was inoculated subcutaneously into a *Macacus cynamalgus*. The monkey did not show any symptoms nor become jaundiced during the succeeding 5 months, nor was the serum collected at intervals icteric. Serum from a single early case was injected subcutaneously into another monkey with negative results. Filtered sterile duodenal contents were also inoculated onto the choroallantois and into the amnion of 12-day chick embryos. The livers of embryos inoculated by the latter method showed some changes, but these were just as marked in controls inoculated with duodenal content from normal individuals.

Because of the uncertainty of the nature of the jaundice when it first appeared, the question arose in the minds of some medical officers whether it was due to leptospiral infection. Agglutination tests were, therefore, performed with the serum of 25 typical cases, using five strains of leptospira, *L. icterohæmorrhagica, Australianis A and B, pomona,* and *mitis*. All were completely negative.

The prolonged action of morphine and of the barbiturates in these patients was very striking. A dose of 1½ to 3 gr. of amytal or 1½ gr. of sodium pentobarbital frequently would cause extreme drowsiness for 24 to 48 hours. The use of any barbiturates was, therefore, abandoned, and morphine used only when absolutely necessary and then in half the dose that would have been used for a non-jaundiced patient. No definite abnormal reactions to codeine were observed. This drug controlled the restlessness of severe cases satisfactorily without significant depression of respiration.

Because of the common exhibition of magnesium sulfate in "catarrhal jaundice" and its alleged action as a cholagogue, it was given to a group of 21 patients in 15-gm. doses each morning before breakfast. Another group of 21 patients, admitted on the same day to the same ward, served as control. All were treated alike in other respects. No difference in the two groups could be detected in symptoms, rate of clearing of jaundice, or decrease in the size of the liver.

The majority of the patients who could eat were given a low fat-high carbohydrate diet containing approximately 450 gm. carbohydrate, 80 gm. protein and 45 gm. fat. Those with little anorexia were allowed the regular hospital diet. The rationale of fat restriction rests on reasonably firm evidence. The merit of restricting protein is less sure. The work of Whipple, Ravdin, and others would suggest that a high protein intake should afford the greatest protection to the liver from the noxious agent. Some patients, however, refused to eat meat, while others apparently experienced no discomfort from it. Of 81 patients questioned particularly about their ability to eat meat since the onset of their jaundice, 61 (75%) had eaten it regularly with no discomfort or aversion, whereas 25% had been unable to do so. Nor

was there any difference in their appetite for different meats. The return of appetite usually followed a characteristic pattern. The patient would be hungry for breakfast, which he would eat avidly and without discomfort. Lunch was less appealing, and might be followed by mild epigastric discomfort, while supper was repulsive, and what little was eaten was apt to be followed by epigastric discomfort, cramps, nausea, and at times, vomiting. This could not be wholly attributed to the character of the foods served at the different meals, for it occurred also in patients on special diets receiving the same foods at all meals. These patients are unable to eat much at one time. Frequently an adequate caloric intake can be maintained and nausea avoided by giving small quantities of food at 2-hour intervals, similar to the routine used in an active peptic ulcer.

While the advantage of high carbohydrate diets in the milder cases is problematical, the value of glucose in the severer cases seemed very definite from clinical observation. Glucose (200 gm. intravenously as a 10% solution in the course of 24 hours) not infrequently transformed a miserable, nauseated, vomiting patient into one in reasonable comfort and able to take food by mouth. Physiologic salt solution alone did not have this effect. In patients with severe anorexia and nausea, the administration of 200 to 300 gm. glucose daily in fruit juice seemed to be of definite value in shortening the period of discomfort. Unfortunately this rests only on clinical impression, as controlled groups were not attempted. In 2 cases of coma the improvement after intravenous glucose was striking. It seemed that 200 gm. daily was about the minimum from which any benefit appeared. While this exhibition of glucose certainly was followed by symptomatic improvement, this does not constitute evidence that it had any direct effect on the hepatitis.

The severer cases received thiamin hydrochloride, thiamin hydrochloride and nicotinic acid, or polyvitamin tablets empirically. There was no evidence apparent of any particular benefit. Atropine, extract of belladonna, and magnesium oxide appeared to give relief in some patients with epigastric discomfort, but not consistently. A few patients with low plasma proteins, and 2 with severe anemia the result of hemorrhage, received blood transfusions.

With the marked anorexia, weight loss was rapid at the beginning of the disease. This was usually about 10 pounds; in the severer cases from 20 to 30. While return of appetite and gain in weight usually coincided, this was not always so. In such patients gain in weight afforded the better indication of progress.

While in the milder cases convalescence was quite rapid, in the severer ones it was prolonged. Frequently there would be complaint of right upper quadrant pain or "heavy feeling" particularly on exertion for several weeks after the jaundice had disappeared. Symptomatic cure was more closely correlated with a negative flocculation test than with disappearance of jaundice. The average period of hospitalization was 29.5 days. One hundred and twelve patients remained 1 to 2 months, while 25 were in hospital more than 2 months.

No late sequelæ have been observed in this hospital. Four of these protracted cases deserve brief mention.

Case Histories. Case 1. E. C., 22 year old white male, received yellow fever vaccine March 15, 1942, developed nausea, vomiting and dark urine on May 20, and jaundice 4 days later. The liver was enlarged 3 cm. below the costal margin, he became deeply jaundiced, but appeared to be making the usual satisfactory recovery during the first weeks of July, with definite clearing of his jaundice. On July 23, edema of the face was noted, definite ascites about August 1, and he was admitted to the 4th General Hospital on August 7, 2½ months after the onset of his illness. He was in considerable respiratory distress due to the marked ascites. There was also marked edema of the face and legs, the liver was small to percussion, the blood pressure was 126/80. He was seriously but not critically ill and perfectly rational.

Laboratory Reports at this time showed the following: Urinalysis—faint trace of albumin and bile. R.B.C. 3,830,000; Hb. 65%; differential—normal; icteric index 53; blood urea nitrogen 11 mg. %. Plasma proteins total 5.68 gm. %, plasma cholesterol 175 mg. %; bleeding and clotting time normal. Abdominal paracentesis was done on the 2d day; 2,000 cc. of bile-stained clear fluid was removed, specific gravity 1.014. Following this his condition rapidly deteriorated, and in 24 hours he was in complete coma, with incontinence of urine and feces, and marked fruity odor to the breath.

He was treated with intravenous glucose, saline, blood plasma and large doses of thiamin chloride and nicotinic acid. After 4 days in coma his condition improved and within a week he was rational and taking food by mouth. The abdominal paracentesis incision continued to drain profusely until about August 22, when it sealed over. No demonstrable ascites was present at this time and patient's condition was good. Within a week, moderate ascites recurred. At this time plasma proteins showed total 5.02 mg. %, albumin fraction 1.51; globulin 3.51; A/G ratio 0.4. He was given 1500 cc. of plasma in a period of 5 days and maintained a diuresis of 3000 to 4000 cc. for 1 week, and in 10 days was edema-free. This marked diuresis was unaccompanied by any significant rise in plasma albumin value, the A/G ratio not returning to a normal figure until 3 months later. The cephalin cholesterol test first taken on August 10 remained positive until October 15. Hippuric acid excretion test was 3.46 gm. in 4 hours on November 10. He was sent back to full duty on November 26, 1942, 6 months after the onset of his illness.

This case is reported in detail because it shows apparent good recovery following severe alteration of liver function, with coma lasting nearly a week. At no time was there evidence of disturbed kidney function and the level of icterus was always moderate.

Case 2. W. R., sergeant, aged 53, developed anorexia and abdominal distress on July 7, 1942. On July 17, icterus was first noted and shortly thereafter ascites. He was admitted to the 4th General Hospital on July 26, 1942. At this time he was deeply jaundiced, icteric index 185, and showed marked ascites with some edema of the legs. The liver was 6 cm. below the costal margin and tender. The heart and blood pressure were normal. Urinalysis and blood counts were normal; plasma proteins total 6.6 gm. with a normal A/G ratio. Cephalin flocculation test gradually decreased from 4+ on July 27 to 1+ on September 30. The ascites gradually disappeared during the month after admission, but he continued to have digestive symptoms and failed to gain strength. He was evacuated to the United States.

This case developed ascites within 3 weeks of the onset of his disease, in the presence of normal plasma proteins. It seemed probable that portal obstruction was the major factor in production of the ascites.

CASE 3. E. B., corporal, aged 28, developed generalized urticaria followed by anorexia, nausea and vomiting, about June 1, 1942. Jaundice appeared 2 weeks later and he was admitted to the hospital. He made an uneventful recovery and was discharged to duty July 22. Though he did not appear icteric, icteric index on day before discharge was reported as 23.

He was readmitted to the 4th General Hospital on October 2, 1942. He had failed to gain weight and strength and had been noticed to be jaundiced on occasions. He had also developed dyspepsia and pain in the right upper quadrant. At this time gastro-intestinal and gall bladder Roentgen rays were negative. He continued to be weak, failed to gain weight, and icteric index varied between 16 and 30. Cephalin flocculation test was 2+, hippuric acid excretion 2.7 gm. in 4 hours. On January 7, it was recommended that he be returned to the United States. His illness at that time had persisted 7 months.

CASE 4. J. N., private, aged 20, developed crampy abdominal pain, anorexia and jaundice about June 1, 1942. His past history revealed he had had jaundice for 6 weeks in 1938, 1 month in 1939, and again in 1940. During his course in this hospital extensive laboratory procedures failed to find any cause for recurring jaundice. He failed to gain weight and strength, dyspepsia continued, and icteric index remained about 20. On January 8 he was recommended for return to the United States 7 months after the onset of symptoms.

These 2 cases, from their duration alone, can be classed as subacute or chronic hepatitis. There is, however, no real ground for believing that they may not eventually recover. Chronic fatigue, failure to gain weight, and continued dyspepsia, were the prominent clinical features of both, as they were in a number of other protracted cases. Also a noteworthy feature was the behavior of the icteric index, which dropped in the usual time to a level of about 20, but then failed to return to the normal base level.

There were 2 deaths in this series of 405 patients, a mortality of 0.49%. While the pathologic changes undoubtedly are primarily the concern of the Army Institute of Pathology, they are appropriately considered here also. The first (Case 5) demonstrates the gradual development of liver insufficiency and the value, albeit temporary in this instance, of glucose. The second (Case 6) was one of rapidly developing liver insufficiency in a man who, although probably jaundiced, had been on duty until some 48 hours before death. Fortunately no cases of sudden death during convalescence, similar to those recorded by Martin,[12] were encountered. One man, however, symptom-free, and with no apparent jaundice, who undertook to walk up several flights of stairs without permission, developed dyspnea, tachycardia and substernal pain which persisted for 24 hours.

CASE 5. W. A. G., aged 21, was admitted June 22, 1942, complaining of abdominal pain. The date of yellow fever vaccination and lot number were not available. He had anorexia and nausea since about June 1, and vomited on one occasion while in the field. Jaundice appeared about June 12, and he was admitted to another Army hospital. On admission here his temperature was 98.2° F., pulse 60, respiration 18. He was coöperative, mentally clear, and did not appear in any acute distress. The skin and sclera were deeply jaundiced. Blood pressure was 90/70. The liver was palpable 2 cm. below the costal margin and was tender. The remainder of the physical examination was normal. His urine had a specific gravity of 1.020, contained 2+ albumin, no sugar, casts or abnormal sediment. Icteric index was 110, sedimentation rate 6 mm. per hour. He seemed to be progressing satisfactorily for a week. Then his jaundice became much deeper, he completely lost his appetite, and com-

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plained of severe abdominal cramps, constipation, weakness and vomiting. He became very somnolent, confused, and finally impossible to arouse. The liver was no longer palpable. Urine sp. gr. 1.015, trace of albumin, no sugar, bile pigments but no bile salts. Hb. was 90%, R.B.C. 5.8 million, and W.B.C. 9000 (65% neutrophils, 30% lymphocytes), icteric index 245, blood non-protein nitrogen 38 mg. per 100 cc. Spinal fluid was faintly but definitely icteric, contained 26 mg. protein and 19 cells (7 neutrophils, 12 lymphocytes) per 100 cc. The Ross Jones test for globulin was negative. He was given 300 gm. dextrose, 50 mg. thiamin hydrochloride and 100 mg. nicotinic acid with 4000 cc. fluid intravenously daily for the next 5 days. He showed considerable improvement. He became conscious and was able to take fluid and food by mouth. On July 16, blood non-protein nitrogen was 33, urea nitrogen 11, sugar 102 mg. per 100 cc. Plasma proteins were reduced to 4.95 gm. per 100 cc. Plasma CO_2 combining power was 63 vol. per 100 cc. The urine continued to show albumin. The white count had risen to 18,000 with 80% neutrophils. There was no anemia. Bleeding time 3 minutes, clotting time (tube method) 17 minutes 25 seconds. Patient continued to be fairly alert mentally and to take sufficient fluid and carbohydrates by mouth, so that infusions were discontinued. He developed marked abdominal distention and some ascites. Abdominal paracentesis was performed on July 22, removing 1600 cc. He was given 500 cc. plasma intravenously on July 21 and again the next day. At this time he was taking 300 gm. carbohydrate and 90 gm. protein daily. By July 27, he had again become delirious and irrational and intravenous glucose, fluid and thiamin hydrochloride were resumed. He showed some purpuric spots but no gross hemorrhage. He lapsed into deeper coma. On August 2, temperature and pulse rate began to rise and he died August 3, with a final temperature of 105° F., pulse 150. Shortly before death blood non-protein nitrogen was 38, urea nitrogen 17, and sugar 100 mg. per 100 cc.; CO_2 combining power 62 vol. per 100 cc. and plasma proteins 4.9 gm. per 100 cc., icteric index 166. Urine volume was in excess of 700 cc., specific gravity 1.009 and it contained a trace of albumin but no sugar.

At AUTOPSY all tissues and organs were deeply jaundiced. There was 2000 cc. bile-stained fluid in the peritoneum. The *liver* weighed 960 gm. It was firm, nodular, and the edges were thin and sharp. The capsule was thin and the surface reddish yellow, with numerous large and small nodular areas which were yellowish green. It cut with considerably increased resistance. The normal pattern was replaced by large bulging nodules which were yellowish green and raised above the surrounding liver tissue. Between these nodules of regenerating and necrotic tissue there were flat, reddish brown zones in which the normal architecture was preserved. The bile ducts presented a normal appearance. The *kidneys* weighed 200 gm. each, with a smooth dark red and yellow surface. The cut surfaces were moist, bulging, and the cortex was considerably increased, measuring 12 mm. in width. The differentiation from medulla was indistinct. There was confluent bronchopneumonia in the lower lobes of both *lungs*. The *stomach, small and large intestines*, showed moderate edema of the mucosa with occasional small areas of hyperemia and a few petechiæ. The *other organs* presented no significant gross abnormality. There were multiple varices in the mesentery, mesocolon and posterior peritoneum, but not elsewhere.

MICROSCOPIC EXAMINATION.—The *liver* showed an extremely variegated appearance. The large nodules were regenerated tissue in which the architecture was fairly well preserved. The liver cells were arranged in cords, were large, and showed numerous mitoses and multinucleated forms. The periportal tissue was increased in some areas and showed proliferation of bile ducts, but no pseudo-lobule formation. In other areas there was extensive necrosis, principally central, but also involving the peripheral zones of the lobules extensively. The necrotic liver cells had been replaced by fibroblasts and well-vascularized young connective tissue. Other areas showed degenerative changes in the liver cells, swelling, vacuolization and pigmentation. None of the cells showed focal hyaline necrosis, and there was only an occasional

ochre cell. A conspicuous change was plugging of bile ducts and canaliculi with large masses of bile pigment, at times with infiltration of neutrophils and lymphocytes. Many cells in regenerated areas were stained with bile pigment. Sections stained with Sudan IV showed only small amounts of fat, principally around the central veins in regenerated areas.

The normal architecture of the *kidneys* was preserved. The glomeruli were normal. The tubules were the seat of marked disease, focal in character, involving principally the ascending limb of Henle and the distal convoluted tubules. These contained large pigmented casts, often mixed with neutrophils, leukocytes, lymphocytes and degenerated epithelial cells. The tubular epithelium was denuded in many places, in others replaced by flattened cells. The interstitial tissue, especially in the pyramids, was slightly edematous with sparse infiltration of lymphocytes in some areas. Fat stains showed marked fatty degeneration of the proximal tubules.

CASE 6. W. G. B., aged 23, was admitted July 15, 1942, in coma and moderately jaundiced. The only history obtainable was that he had been left in quarters the day before, when his company went on a hike. That evening he was found to be difficult to arouse and was admitted to the station hospital, where he was described as comatose, restless, and entirely uncoöperative. Except for jaundice, the physical examination was normal, the blood pressure 140/80. His urine contained no sugar or acetone. During the night his coma became deeper and he was transferred to this hospital by ambulance the next morning. On admission he was entirely unresponsive, showed periodic respirations, deep jaundice, and a few coarse râles at the base of each lung. Blood pressure was 105/60 and pulse regular at 140 per minute. The liver and spleen were not palpable. Deep reflexes were hyperactive with bilateral sustained ankle clonus. Urine had a specific gravity of 1.018, contained a trace of albumin, no sugar, and a few coarsely granular casts. Hb. 85%, R.B.C. 4.6 million, W.B.C. 12,900 per cmm. (84% neutrophils, 14% lymphocytes, 1% each monocytes and basophils). Non-protein nitrogen was 36 and urea nitrogen 7 mg. per 100 cc. Plasma proteins 6 gm. per 100 cc. Icteric index 140. The spinal fluid was faintly yellow, contained 2 cells per cmm. and 20 mg. protein per 100 cc. He was given 10% glucose intravenously, thiamin hydrochloride and, with the onset of pulmonary edema, intravenous digitalis. He died 9 hours after admission, following several convulsions.

At AUTOPSY all the organs and tissues were deeply bile-stained. There was no free fluid in thorax or abdomen. There were numerous ecchymoses beneath the endocardium of the interventricular system. The *lungs* were deep red, firm and contained considerable frothy bloody fluid. The *liver* weighed 1055 gm. The surface was uneven with slightly raised bright yellow areas. On section, the normal architecture was preserved in some areas, while in others there were irregular areas of coagulation necrosis, yellowish gray in color. The *extrahepatic bile ducts* were normal. The *kidneys* weighed 195 gm. each. On section, the division between cortex and medulla was somewhat indistinct. The pyramids were deep red. There was no edema of the *gastro-intestinal tract.*

MICROSCOPIC EXAMINATIONS. The *liver* showed various appearances. Those from the yellowish necrotic areas showed extensive necrosis with complete wiping out of the normal architecture, so that an amorphous granular material alone remained. In other sections the normal architecture could be distinguished, but was much altered. There was extensive necrosis, more marked about the central veins. Most of the necrotic cells were pale pink staining, but some showed bright red hyaline necrosis and resembled Councilman bodies, while others were ochre yellow and resembled the cells described by Villela.[16] Neither of these changes was very conspicuous, but when searched for were easily found. The intact cells showed some fatty metamorphosis and vacuolization of the cytoplasm, but there were no cytoplasmic or nuclear inclusions. There were moderate numbers of binucleated cells and mitoses. The kidney architecture was preserved and the glomeruli appeared normal. There was marked swelling with vacuolization and granularity of the cytoplasm in the cells of the proximal convoluted tubules. Many of the lumina were closed by swelling of the epithelium.

Both cases thus showed extensive necrosis and atrophy of the liver with varying degrees of fibrosis and regeneration. The necrosis was principally central, although not strikingly so. Both cases showed minimal hyaline necrosis, although occasional Councilman bodies were present. In 1 case there were numerous ochre bodies such as have been described by Villela in cases of yellow fever, where death was delayed, and which, therefore, cannot be regarded as characteristic of that disease. The liver lesion seems indistinguishable from that of "infectious hepatitis" where no yellow fever vaccine had been administered. The changes in the kidneys of the first case seem identical with those seen after transfusion reactions, crush injuries[3] and in deep jaundice[1] (the "lower nephron syndrome").

After an interval of 4 months with only an occasional admission for "jaundice," another epidemic of over 100 cases was encountered among troops returning from the combat zone, who had yellow fever vaccine from 12 to 18 months previously. This group appeared to have a disease indistinguishable from the epidemic jaundice or infectious hepatitis described among civilians and in armies in previous wars. While the spontaneous disease and that following vaccination are extremely similar, certain differences have been noted. The incubation period of the natural disease is usually given as about 30 days. While it was impossible to determine this among the troops, evidence is afforded by 2 cases in the Army Nurse Corps. One nurse had taken special care of the 1 fatal case 19 days before she developed jaundice, while the other had been "out" with an officer who developed jaundice 2 days later. She became jaundiced after 28 days. The average incubation period in the postvaccination cases, on the other hand, averaged about 3 months, corresponding with that described by Findlay in postvaccination jaundice. Fever and upper respiratory symptoms were more frequent in the naturally occurring disease. Forty-eight per cent had fever (above 99° F.) compared with 17% in the postvaccination group. If the usual mode of spread is by droplet infection, this may account for the latter observation. No definite second wave of jaundice was encountered in the postvaccination group; this may also be due to the fact that the noxious agent was introduced by an abnormal route, and that concentration of the hypothetical virus did not occur in the upper respiratory tract. In general, lassitude and malaise were more marked in the natural disease, the onset more abrupt, and convalescence more rapid. Thus the average interval between onset of symptoms and jaundice was 3.1 days, while in the postvaccination disease it was 7.2 days. The average period of hospitalization was only 18.2 days for the natural epidemic, and 29.5 days for the postvaccination cases.

Summary. Clinical observations on 398 cases of jaundice following yellow fever vaccination are recorded. In 183 cases where date of vaccination and jaundice was accurately known, the mean interval was 100.1 days. The symptoms are indistinguishable from those of infectious hepatitis, but the onset more insidious. The mean interval between onset of symptoms and jaundice was 7.2 days. Fever occurred

in only 17%, albuminuria in 18.5%. Leukocyte count, differential count, and sedimentation rates were normal. The mean maximum icteric index was 64.4. The cephalin flocculation test was positive in the 220 cases in which it was performed, and furnished a valuable index of progress. Bile was present in the duodenum of 50 cases intubated at all stages of the disease. There is no evidence that biliary obstruction is a factor in production of the jaundice. The value of dietary treatment in the milder cases is problematical, but the value of glucose in severe cases was quite evident. There were 2 deaths, a mortality of 0.49%. The average period of hospitalization was 29.5 days. Convalescence was prolonged.

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ANAËROBIC SEPTICEMIA

Report of 6 Cases With Clinical, Bacteriologic and Pathologic Studies

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Septicemias due to anaërobic, non-sporeforming bacilli occur in only a small proportion of all cases of systemic infection seen by the clinician. However, the high death rate in such infections warrants that considerable attention be given them in order that an early diagnosis be made and suitable treatment if possible be instituted. In a review of 144 cases of septicemia seen at the Mayo Clinic, Rosenow

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and Brown[11] found that the causative agent in 6 of them was *Bacteroides funduliformis*, and that the fatality rate was 100%. A report by Herrell and Brown[8] on the treatment of septicemic infections before and after the advent of the sulfonamides gives 265 cases, 8 of which were caused by members of the genus Bacteroides. The fatality rate here was also 100%. Observations as to the highly serious nature of Bacteroides septicemias have also been reported by Thompson and Beaver,[13] Dixon and Deuterman[5] and Lemierre.[9]

It is apparent from the above-mentioned reports that no completely satisfactory method of treatment for these infections has been devised. Since thrombophlebitis at the site of the initial lesion is a characteristic finding, ligation of the veins, if accessible, below this area has been suggested as a procedure of possible value as a means of limiting the spread of the infection. Although the sulfonamides have not been particularly effective against anaërobic infections, the successful treatment of a case of Bacteroides septicemia by the use of sulfonamides has been reported by Brown, Williams, and Herrell.[3] They recorded the recovery of the patient by maintaining a high sulfapyridine blood level (14 mg. to 19 mg.), plus multiple blood transfusions. Anderson,[1] using similar therapeutic procedures, noted the recovery of a child with a *Bacteroides funduliformis* septicemia. Both of these cases were treated with sulfonamide compounds from the date of admission to the hospital, and before bacteriologic studies had been made. Goodnough[7] reported the recovery of a patient with a liver abscess from which *B. funduliformis* was isolated. Treatment consisted of incision and drainage of the abscess plus chemotherapy with the sulfonamides. He believed that the sulfonamides contributed to the patient's recovery. It was not determined in this case whether a blood stream infection existed.

In considering the value of the sulfonamides in septicemias due to Bacteroides, the experimental work of Prevot[10] is of interest. Prevot produced septicemias in rabbits by intravenous inoculation of a suspension of *Spherophorus funduliformis* (*Bacteroides funduliformis*). Treatment of these infected rabbits with repeated subcutaneous injections of sulfanilamide resulted in a 76% recovery rate. The disease was invariably fatal in the untreated controls. He concluded that sulfonamide therapy was of definite value if given early, in large doses, and continued until danger of relapse had disappeared.

Since apparent successful therapy of these infections has followed early administration of the sulfonamides, an early diagnosis may be of paramount importance. This can best be made by careful observation of characteristic clinical symptoms and use of satisfactory bacteriologic procedures. For this reason, we are reporting the findings in 6 cases of septicemia due to Bacteroides that we have seen, together with the bacteriologic techniques that have been found satisfactory by us for isolating these organisms.

Case Reports. CASE 1. H. J., a white female, age 20 years, was admitted to the Memorial Hospital on November 3, 1936, complaining of a right-sided headache, double and failing vision. In June, she had developed a sore throat

which was followed by a peritonsillar abscess that ruptured spontaneously into the mouth. This series of events was followed by fever and chills at irregular intervals for several weeks, after which she felt quite well again. In August, she developed a throbbing type of headache associated with spasmodic vomiting spells, which continued throughout the course of the illness. Her vision became less acute than formerly, and at times a double vision was noticed.

A general physical examination was negative. Neurologic examination revealed the following positive findings; bilateral choking of the optic disks; left lower facial weakness; greatly diminished abdominal reflexes on the left and an equivocal Babinski on this side. There was no jaundice or clinical evidence of lung pathology.

On November 6, a well encapsulated abscess in the parietal region was aspirated and about 40 cc. of thick green pus removed. A culture of this pus on anaërobic media showed a growth of *Bacteroides gonidiaformans*. The patient failed to respond to treatment and died on November 24, 1936.

Autopsy Findings. Autopsy, performed 2 hours after death, was limited to the head. The brain showed an area of bulging 5 cm. in diameter in the right occipito-parietal region in which the convolutions were flattened, the meninges dull, and the subarachnoid space contained turbid exudate. On section of the brain after fixation there was a well walled-off abscess 5 cm. in diameter in the right occipital lobe, which extended from the level of the splenium of the corpus callosum almost to the tip of the occipital lobe. The right cerebral hemisphere was markedly swollen and the right lateral ventricle almost obliterated. Microscopic sections from the abscess wall showed organizing granulation tissue containing many newly formed capillaries. The abscess cavity contained a polymorphonuclear exudate. The white matter adjoining the abscess wall showed edema and marked perivascular accumulations of small round and plasma cells.

CASE 2. J. B., a colored male, age 22 years, was admitted to the St. Philip Hospital on July 8, 1937, complaining of fever, chills, night sweats, sore throat and pain in the right chest. He had been expectorating about ½ cup of thick purulent sputum a day. The patient had developed a sore throat on June 25, and had been put to bed by his family physician 2 days later. The above-mentioned symptoms developed rapidly after this time. His past history was entirely negative except for the fact that, in 1934, he had been successfully operated on for a stab wound of the heart at the St. Philip Hospital.

On initial examination, the temperature was 102.8° F., respirations 42 per minute, pulse 112, and blood pressure 144/62. The essential findings consisted of a yellowish discoloration of the scleræ; enlarged, cryptic, and inflamed tonsils; moist râles in both lung bases with bronchial breathing present posteriorly over the lower one-third of each lung, and a liver edge that was felt 2 cm. below the costal margin.

The urine showed a trace of albumin and was positive for bile. The routine blood studies showed no significant findings except for a leukocytosis of 11,850. The non-protein nitrogen was 41, and the icteric index 96.4.

The patient presented a characteristic picture of septicemia. Repeated aërobic blood cultures, however, proved to be negative and the patient died on July 18, 1937, 10 days after admission, with a diagnosis of septicemia, cause undetermined.

Autopsy (3 hours and 20 minutes after death). There was a small abscess in the right peritonsillar region. The veins draining this region were distended and filled with pus as far as their junction with the right internal jugular vein, which in turn was filled with a partly organized thrombus extending downward into the right innominate vein. At its lower extent, the wall of the internal jugular vein was thinned and soft, but showed no perforation. In the soft tissue above the right sterno-clavicular joint, there was an abscess which extended caudally for 2 cm. in the tissue overlying the carotid sheath.

Both lungs were increased in weight (left, 580 gm.; right, 340 gm). Both showed irregular yellowish pink areas with a dark red border raised above

the pleural surface. On section, many of these nodules were coalescent and showed central areas of softening. The larger pulmonary veins contained thrombotic material. Microscopic sections showed typical septic infarcts of the lung and thrombophlebitis of the branches of the pulmonary vein.

The spleen (640 gm.) was very soft. The pulp had the color and consistency of thick red paint and scraped away easily. Microscopically, there was marked congestion of the pulp and sinuses with a greatly increased number of neutrophils in the pulp.

Microscopically, liver and kidneys showed interstitial accumulations of neutrophils, lymphocytes and macrophages with interstitial edema.

Anatomic diagnosis: Peritonsillar abscess, right. Thrombophlebitis of right internal jugular vein and its tributaries, right innominate vein, and pulmonary vein. Septic infarcts of lungs. Acute splenic tumor. Acute interstitial hepatitis. Acute interstitial nephritis. Jaundice.

Although positive bacteriologic findings are lacking on this case, the clinical picture is typical of a Bacteroides septicemia, as described by Sodeman[12] in an excellent résumé of anaërobic septicemias published at this time. Since this case illustrates well the problems involved in making a diagnosis, it is included here.

Case 3. J. K., a colored male, age 24 years, was admitted to the St. Philip Hospital on March 23, 1938, complaining of a sore throat, swollen neck and headache. He had had several chills followed by high fever and diffuse sweats.

On initial examination the temperature was 103° F., respirations 24 per minute, pulse 95, and blood pressure 110/60. The skin and mucous membranes were jaundiced. The tonsillar region and pharynx could not be examined because of trismus. The neck was absolutely rigid to anterior, posterior and lateral motion. Extending downward from the angle of the right mandible and disappearing beneath the clavicle were 2 firm, tender, cordlike structures. Coarse rhonchi were heard over the chest. The liver and spleen could not be palpated.

The urine showed a heavy trace of albumin and the presence of hyaline casts. The blood count was not significant, although there was a leukocytosis of 25,000. The blood chemistry showed a non-protein nitrogen of 113 mg., and an icteric index of 134. The Wassermann and Kline tests were positive. There were 1670 W.B.C. in the spinal fluid, with 96% neutrophils. A portable Roentgen ray of the chest showed irregular mottling extending from both hilar regions. A blood culture taken on March 25 was subsequently positive for *Bacteroides gonidiaformans*.

The patient was given 6 gm. of sulfanilamide in normal saline by hypodermoclysis on March 24, and 10 gm. by the same method on March 25. In addition, glucose and saline were given intravenously as general supportive treatment. None of these therapeutic measures seemed to influence the course of the disease, and the patient died on March 25, 1938, 3 days after entering the hospital. Permission for autopsy was refused.

Case 4. L. A., a white female, age 20 years, was admitted to the Medical College Hospital on April 21, 1941. Three weeks prior to her admission she had a tonsillitis which had developed into a peritonsillar abscess. Two weeks before entering the hospital she had chills with high fever and a swelling of the right side of the face. Her right eye had become swollen shortly after this. Because of the fact that she had failed to respond to treatment with sulfathiazole, she was referred to the hospital.

On admission, her temperature was 103° F., respirations 24 per minute, pulse 120, and blood pressure 124/80. The right eyelid was swollen and closed, and the right pupil was widely dilated. The fundus was normal. The tonsils were moderately injected, but no purulent exudate was noted. No pathologic findings were noted in the chest, heart or abdomen.

The urine was negative. Examination of the blood showed a slight hypochromic anemia. There was no leukocytosis. The icteric index and nonprotein nitrogen were normal.

One week after admission, she developed a septic arthritis of the left shoulder,

and 25 cc. of thick, green pus was aspirated, from which was grown *Bacteroides funduliformis*. Blood cultures taken on April 28 and 30 were also positive for this organism. On May 2, there was Roentgen ray evidence of multiple infarction in the lung. Three days later, she was explored for a brain abscess with negative results.

Treatment, in addition to general supportive measures and repeated blood transfusions, consisted of chemotherapeutic measures. Oral administration of sulfathiazole was started on April 21, and 3 days later a blood level of 3.2 mg. per 100 cc. was obtained. Since there appeared to be no improvement in her clinical state, the drug was discontinued and, on April 28, treatment begun with sulfapyridine. On April 29 and 30, the oral dose of sulfapyridine was supplemented with sodium sulfapyridine given intravenously. The blood levels were recorded as being 15.4 mg. and 17.3 mg., per 100 cc. on April 29 and 30, respectively. Neither of these drugs influenced the course of the disease and the patient died May 8, 1941.

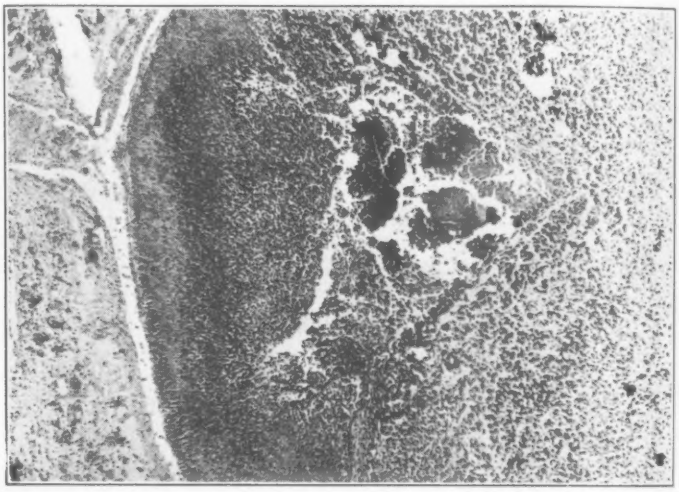

FIG. 1.—Section of lung showing at the left, the wall of a branch of the pulmonary vein with a small tributary. The vein lumen is filled with a thrombus containing many neutrophils. On the right the wall of the vein is completely destroyed and the lumen is continuous with an abscess in the lung parenchyma showing an area of softening. (Hematoxylin and eosin, × 90.)

Autopsy (2 hours postmortem). There was an open 6 cm. wound of the left shoulder anteriorly with a small amount of thick purulent yellow drainage. Both lungs contained well-defined nodular areas of consolidation. On section some of these areas showed soft necrotic or frankly purulent central areas. The visceral pleura immediately overlying these areas was covered with fibrin. Microscopically, many of the branches of the pulmonary vessels were filled with thrombi, some of them undergoing organization. Areas of hemorrhage into the alveoli with necrosis of the alveolar walls, characteristic of infarction, were present. Some of these showed accumulations of neutrophils with necrosis and liquefaction. (See Fig. 1.)

Spleen weight, 210 gm. On section the cut surfaces bulged and the pulp scraped away easily. Microscopic sections showed congestion of the pulp by R.B.C. and a markedly increased number of neutrophils. No abscesses were present.

The entire base of the brain was covered by a thick yellow purulent exudate lying in the subarachnoid and subdural spaces and extending posteriorly over

the tentorium cerebelli and involving most of the cranial nerve roots. The cerebellum showed no gross changes.

The pituitary was increased to three times its normal size. The pituitary fossa was increased in size and covered by purulent exudate. The sphenoid and ethmoid sinuses contained purulent material.

Microscopic sections of the brain showed a fibrinopurulent meningitis with early necrosis of the exudate. The walls of the meningeal vessels were infiltrated by neutrophils. Within the white matter there was moderate perivascular infiltration of neutrophils. Sections of the pituitary showed fibrinopurulent exudate surrounding the gland and small focal areas of necrosis just beneath the capsule.

Anatomic diagnosis: Fibrinopurulent basal meningitis, more marked on right. Purulent sinusitis of ethmoid and sphenoid sinuses. Osteomyelitis of pituitary fossa. Multiple bilateral embolic pulmonary abscesses. Thrombophlebitis of pulmonary veins. Draining subcutaneous abscess of left shoulder region. Acute splenic tumor.

At autopsy, *Bacteroides funduliformis* was isolated from the spinal fluid and *Bacteroides funduliformis* and *Staphylococcus aureus* were isolated from a brain abscess and from the lung.

CASE 5. L. P., a colored male, aged 41, was admitted to the St. Philip Hospital on August 24, 1941, complaining of pain and swelling in the right knee and left elbow. The joint pains had begun about 3 weeks prior to this date and had affected both knees, wrists, and elbows. This general involvement had gradually subsided and the pain became localized in the right knee and left elbow. For 1 week, he had noted progressive swelling of these joints. Throughout the period of this illness, he had been troubled with an extremely sore throat. Ten days before entering the hospital he had expectorated a mouthful of thick pus.

On initial examination, the temperature was 102.8° F., respirations 24 per minute, pulse 120, and blood pressure 125/75. The patient was well developed and well preserved, rational and alert. The mucous membrane of the throat was extremely hyperemic and somewhat edematous. Several small superficial ulcers were present on both tonsils. The chest, lungs and heart were normal. There were no masses, palpable organs or areas of tenderness in the abdomen. The left elbow and right knee were swollen, tender, hot and painful to touch and passive motion.

The urine was negative. The routine blood studies showed a moderate hypochromic anemia and a leukocytosis of 13,750. The Wassermann and Kline tests were positive.

The clinical course was characterized by a constant temperature elevation varying from 99° to 104° F. until September 3, when it became normal and remained so until his discharge. This was associated with a tachycardia of from 90 to 120 per minute without arrhythmia. There were no chills or profuse sweats. On August 24, the right knee was aspirated with the removal of 15 cc. of thick foul pus which had an odor resembling rancid butter. A culture of this fluid was reported positive for *Bacteroides funduliformis*. Two days later the left elbow was aspirated and pus of a similar nature removed. A similar organism was isolated from this fluid. At this time, it was noted that the left side of the neck was beginning to swell and that the area involved was hot and tender. On August 28, a Roentgen ray examination was made of the cervical vertebræ. The report indicated the presence of a small swelling at the level of the 5th and 6th vertebræ which was thought to be a retropharyngeal abscess. Blood cultures were consistently negative, but an agglutination test using the patient's serum against the organism isolated from the knee was positive in a 1 to 80 dilution. On September 3 a large, left cervical abscess was incised and drained with the evacuation of a large quantity of thick pus. Bacteriologic studies on this showed the presence of *Bacteroides funduliformis*.

Treatment consisted of general supportive measures as regards food and fluid. Sulfathiazole was given daily from August 24 to September 4. Blood levels of 2.6 mg. and 7 mg. per 100 cc. were obtained on September 1 and 3,

respectively. After this time, the medication was changed to a saturated solution of potassium iodide. This was discontinued on September 16, 1941.

The patient's hospital course was uneventful thereafter, and he was discharged on October 20, 1941, apparently well.

CASE 6. H. L., an acutely ill, white, male, age 23 months, was admitted to the Medical College Hospital on October 4, 1941. A few weeks prior to this date he had developed a diarrhea associated with persistent vomiting. These symptoms had lasted for 1 week. Following this he developed a sore throat and the anterior cervical lymph nodes became markedly swollen and tender. On September 27, 1941, the child began to have a hard shaking chill daily and this continued until the day of admission.

On initial examination, the temperature was 102.8° F., respirations 36 per minute, pulse 136. The skin was hot and dry, but clear. There was a small hemangioma over the left temporal area. The anterior, cervical lymph nodes were found to be slightly enlarged, but not tender. The chest, lungs and heart were negative. The abdomen, extremities, and neuromuscular apparatus were normal upon examination.

Routine examination of the urine was negative. The blood showed a persistent and severe hypochromic anemia (hemoglobin 50%, R.B.C. 3,320,000) and leukocytosis of 26,000. Routine aërobic blood cultures were negative.

After hospitalization, the clinical course was characterized by the daily occurrence of hard, shaking chills with profuse sweats. These were associated with temperature elevations varying between 104° and 107° F. On October 4, an anaërobic blood culture was reported positive for *Bacteroides funduliformis*. This finding was confirmed by a second blood culture on October 15. There was little change in the general clinical behavior until October 13, when many coarse râles were heard in both lung fields. Roentgen ray studies made on October 15 revealed an extensive irregular mottling of the lung fields suggesting bronchopneumonia.

Treatment consisted of general supportive measures in regard to diet and liquid. In addition, 3 blood transfusions of 250 cc. each of citrated blood were given. Sulfadiazine was used intensively from the time of admission in relatively large doses until October 17, when the blood level was found to be 20.1 mg., at which time numerous crystals were found in the urine.

On October 18, the temperature suddenly returned to a normal level and thereafter remained normal. The patient was discharged from the hospital on November 1, 1941, apparently completely cured.

Bacteriological Studies. The species of organisms responsible for these anaërobic septicemias are members of the genus Bacteroides. They are found, as mentioned by Dack,[4] "as normal inhabitants of the mucous membranes of the body, inhabiting the upper respiratory tract, the colon and the genital tract." Infection occurs after damage to the mucous membranes, which allows the organism to gain a foothold in the tissues. Certain other conditions are probably essential in order that infection may take place, since most of these species appear to have a low degree of invasiveness. Lemierre has mentioned that a thrombophlebitis is a common finding at the site of the initial invasion, and possibly the stasis of blood brought about as the result of this establishes conditions which are suitable for the multiplication of these anaërobes.

The organisms may be cultivated either from the blood or from the metastatic abscesses which occur. Such cultivation depends upon the use of a media enriched with body fluids and suitable anaërobic conditions. We have found that many of the non-sporeforming anaërobes will grow well in veal infusion, 0.3% semisolid agar, containing 0.5%

sodium citrate and 0.3% dextrose. This media is put into 125-cc. Erlenmeyer flasks in 60-cc. amounts and is used routinely in our laboratories for blood culture work. The blood of the patient in this case taking the place of the body fluid needed for enrichment of the media.

Growth of Bacteroides occurs at the bottom of the flask, and may first appear within 2 to 4 days, depending upon the number of organisms in the initial inoculum. Morphologically, they are gram-negative, non-sporeforming bacilli with a great tendency to pleomorphism and irregularity in staining. They appear in culture as very short and/or filamentous rods. In pus from abscesses, the short forms predominate. The latter forms appear bipolar when stained by Gram's method. The long forms show irregular stained areas, at times giving a beaded appearance to the organism. *Bacteroides gonidiaformans*, the organism isolated from 2 of the cases differs in morphology from *Bacteroides funduliformis* in that, as stated by Bergey,[2] "gonidia form within the rods, developing into short or long wavy filaments." The characteristic morphology of these organisms as described above, together with their anaërobic growth requirements, is sufficient to warrant a preliminary bacteriologic diagnosis while further cultural and pathogenicity studies are being carried out.

Surface colonies can be obtained later by using any of the well known methods for anaërobic cultivation of bacteria and are best obtained when fresh blood agar slants are used. The colonies are small, convex and greyish in color. When inoculated into chopped meat tubes, there is a slight gas formation with the development of a foul odor, but no apparent digestion of the meat. Acid and slight gas production occurs in dextrose. Lactose and saccharose are not fermented. Gelatin is not liquefied and no growth occurs in litmus milk.

Intraperitoneal inoculation of saline suspensions of cultures of *Bacteroides funduliformis* into guinea pigs resulted in the production of a purulent, fibrinous peritonitis with death of the animals usually within 48 to 72 hours. Localized abscesses developed when the organisms were inoculated subcutaneously into mice. Usually the abscesses healed spontaneously.

It is of interest to note that agglutinins appear in the blood of infected individuals. Blood serum for serologic tests was obtained from 2 of the patients. On the 4th day after admission, a blood agglutinin titer of 1 to 80 was obtained on Case 4, using the organism isolated from the patient as an antigen. One week later the titer had risen to 1 to 320, and was still at that level 2 weeks later, the last time that blood was obtained. A blood specimen from Case 5 obtained 3 days after admission, gave an agglutinin titer of 1 to 320 against the homologous organism. Cross-agglutination studies with these 2 strains indicated that they were antigenically similar. Agglutination studies were not carried out on the other patients. Both of the above-mentioned cases recovered. Case 4 had been treated with sulfathiazole and potassium iodide, and Case 5 with sulfadiazine and multiple blood trans-

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fusions. Whether the appearance of antibodies may have played a part in the recovery is not known.

Comment. Septicemias due to organisms of the genus Bacteroides arise from inflammatory or suppurative lesions in the tissues or body cavities where the organisms live under physiologic conditions. Here they grow and multiply, invade the regional veins and produce a thrombophlebitis, frequently giving rise to septic emboli which are borne to distant areas. The sites from which these organisms are most apt to invade the blood stream are the tonsils and peritonsillar regions, the middle ear and mastoid, teeth and gums, the appendix, the uterus and pelvic organs, and the prostate. Of these, peritonsillar abscesses are by far the most frequent source of infection.

Probably the most characteristic finding in this type of lesion is the thrombophlebitis which occurs in the veins draining the area of suppuration. The work of Fraenkel[6] in Germany, in 1926, pointed out the universal occurrence of this type of lesion which, at times, was limited to the peritonsillar veins, but often extended out to invade the external and internal jugulars. Thrombophlebitis offers a valuable clinical sign in anaërobic infections of the structures of the head and throat, particularly since suppuration is often not clinically visible, as in the cases of deep peritonsillar abscesses. When the original site of infection lies in the prostate, appendix or uterus, the clinical value of this pathologic condition disappears. Not only is the thrombophlebitis a valuable physical sign, but it is also the characteristic pathologic lesion, and offers the basis on which this type of septicemia differs in part from the septicemias usually encountered in aërobic infections.

Infected emboli are dislodged from the main thrombus, and are disseminated through the body. The first organs involved are naturally the lungs. Multiple septic infarcts soon break down into multiple abscesses, producing such symptoms as dyspnea, expectoration, chest pain and cough, and such physical signs as coarse, moist râles, and scattered areas of consolidation. Occasionally empyema results. From these areas in the lungs, secondary, infected, emboli arise to be carried to diverse areas in the body, the most frequent sites of lodgment being: (1) The liver; where the lesion may be a single or multiple abscess or a diffuse hepatitis as in Case 2. Clinically, as in our case, jaundice of a severe nature may result. (2) The joints; the patient may complain of severe generalized joint pains without presenting objective findings. In other cases, massive suppurative lesions of the joint may occur. (3) The kidney; embolic nephritis with albuminuria, casts, W.B.C. and reduced renal function may result. (4) The brain; an embolic encephalitis results which often localizes with the formation of a brain abscess, as in our Case 4.

The general reaction of the patient is characterized by fever, chills, and profuse sweats, with wide variation in temperature readings over a 24-hour period.

In treatment, general supportive measures, such as fluids orally and parenterally, and repeated blood transfusions, are essentially necessary. The ligation of the neck veins below the area of thrombo-

phlebitis is of possible value. Necessarily, this procedure can be adopted only when the veins are accessible and when metastatic lesions have not been established. The early use of high blood levels of the sulfonamides, together with multiple blood transfusions may be of value in these infections. Encouraging results have been reported in 2 cases[1,3] in which this therapeutic procedure has been instituted, but we have also recorded 1 case in which sulfathiazole and sulfapyridine plus blood transfusions were used, which terminated fatally. This case was further complicated by a *Staph. aureus* septicemia, which may have influenced the outcome. One other case in our group, which was treated with sulfanilamide alone, terminated fatally. The efficacy of this mode of treatment will depend upon the results obtained after further trial.

The successful and early laboratory diagnosis of these infections depends to a large extent upon the information given to the bacteriologist by the clinician. Anaërobic cultures should be suggested in cases of suspected septicemias which have clinical symptoms similar to those mentioned above, and where aërobic cultures are consistently negative. Obviously a simple media suitable for the growth of both aërobes and anaërobes would be of distinct value to the bacteriologist. We have suggested such a media, which, while we make no claims as to originality, has been used satisfactorily by us for the cultivation of anaërobes of the genus Bacteroides from the blood.

The morphologic characteristics and the anaërobic nature of these organisms, as seen in the initial culture, is often sufficiently striking to warrant a tentative bacteriologic diagnosis of Bacteroides septicemia. Therapeutic measures may then be instituted while further biochemical and agglutinative studies on the organism are being performed.

Agglutinins are formed during the course of the infection and might serve as a means of diagnosis where there has been failure to isolate the specific organism. We have been able to demonstrate such antibodies in the 2 cases from which blood was obtained for this purpose. Since both of these cases recovered, it is interesting to speculate upon the possibility of the part they had in the recovery of the patients. However, we did not obtain blood serum for agglutination from the other cases which terminated fatally.

Conclusions. The non-sporeforming, anaërobic bacilli of the genus Bacteroides invade the blood from certain focal areas in the body where these organisms live habitually.

The most characteristic pathologic symptom is a thrombophlebitis of the regional veins, which occurs in all cases. From this source, the infection is disseminated throughout the body by means of septic emboli.

The detection of such infections depends upon the careful observation of certain characteristic symptoms and the use of suitable cultural technique for the isolation of the organisms.

Agglutinins appear in the blood stream of infected patients, and may serve as a means of diagnosis where there is failure to isolate the organism.

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Early treatment by means of high levels of the sulfonamides together with multiple blood transfusions appears to offer possibilities as a successful mode of therapy in these highly fatal septicemias and is worthy of further trial.

Since this paper was written two additional reports have appeared on Bacteroides infections treated with sulfonamides. These cases are described elsewhere.[14, 15]

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THE COINCIDENCE OF ALLERGIC DISEASE, UNEXPLAINED FATIGUE, AND LYMPHADENOPATHY; POSSIBLE DIAGNOSTIC CONFUSION WITH INFECTIOUS MONONUCLEOSIS*

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A group of cases with uncontrolled clinical allergic manifestations whose major complaint was fatigue was recently studied by one of us (T.G.R.) in conjunction with Elizabeth Barber Gibson.[5] The fatigue or weakness in these individuals was unrelieved by what is ordinarily considered an adequate amount of rest. Rowe[7,8] recognized this complaint as an expression of the allergic reaction, giving it the descriptive term of "allergic toxemia." Our observations agreed with those of Rowe in that this symptom occurred most commonly in association with some other allergic manifestation, more frequently in women than in men, and usually the result of allergic intolerance to foods. Significant numbers of atypical mononuclear cells were observed in the peripheral blood of many of these cases. These cells, identical with the atypical lymphocytes observed in infectious mononucleosis and best described by Downey,[2] comprised as high as 25% of the

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differential count. Although such cells were distinctly less in number than is commonly seen in the acute stage of infectious mononucleosis, the blood findings in the allergic individuals were compatible with the subsiding phase of glandular fever.

Infectious mononucleosis was often suspected in patients with allergic disease because of the complaint of fatigue, the finding of atypical lymphocytes in the differential counts, and the not infrequent past history or physical finding of tender, swollen cervical glands. Confusion in the differential diagnosis of allergic disease and infectious mononucleosis was further heightened by the common age incidence of the two manifestations. Both occur in young adults otherwise in the best of health and at an age, generally speaking, when the individual's immune response is most vigorous. Repeatedly negative heterophil antibody determinations had been found in several of these cases prior to their coming to our attention for an allergic study. Negative titers were again obtained at the time of their allergic investigation.

Independently, one of us (R.A.H.) had noted the presence of atypical mononuclear cells in the differential white cell counts of approximately one-fifth of the Freshman nursing class of 75 in the course of routine blood examinations. These cells also had the characteristics of the atypical lymphocytes observed in infectious mononucleosis. Upon the basis of this finding alone, several were suspected of having infectious mononucleosis, but heterophil antibody determinations were negative, with the exception of 1 case. This individual, subject to bronchial asthma and allergic rhinitis, was found to have a positive titer in a dilution of 1/2048; she also had the clinical features of infectious mononucleosis including extreme fatigue and a generalized lymphadenopathy. At the time she had a total leukocyte count of 17,100 and a differential count of 18% polymorphonuclear leukocytes, 69% large lymphocytes, of which practically all were atypical forms, 7% small lymphocytes, and 6% monocytes. Her blood was followed at monthly intervals and the number of the atypical lymphocytes slowly returned to normal.

The opinion was expressed that several of the other cases having atypical mononuclear cells at the time of their examination may have been in the recovery or residual phase of infectious mononucleosis, or that an epidemic of that disease had been present in the nurses' dormitory. This did not seem probable, since similar blood variations had been noted in the survey of the incoming class the preceding year.

As a consequence to these independent observations in groups of allergic and "normal" individuals, we recorded an allergy history, and repeated the blood counts in the same group of nurses a year after their earlier examinations. Each member of the 2 upper classes in the Nursing School was studied, a total of 140 cases. In addition, the individual hospital records were reviewed to determine whether the diagnosis of infectious mononucleosis had ever been suspected. Each matriculating student nurse had been subjected to a complete physical examination, and about 5% of them had been rejected because of some

physical disability. The group of student nurses had remained under very close medical supervision, since they were required to report to the Medical Clinic in the event of even minor illnesses.

In obtaining the allergy history, each person was asked whether she had been subject to periods of fatigue, unrelieved by the customary amount of rest. This admittedly was a difficult question; the answer depended in large part upon the amount of work performed and the amount of sleep obtained. However, under the carefully regulated conditions of nursing training the amount of work was approximately the same for each individual, and each person was required to live in a dormitory where strict rules regarding the time of reporting for duty and retiring were enforced. Under these circumstances, reasonably reliable answers to this question might be expected.

Each individual was asked whether she had had tender, swollen cervical glands, and if so whether this had occurred with or without accompanying upper respiratory infections. The nurses were also asked whether or not they had ever been suspected of having infectious mononucleosis or glandular fever. It might be added that this query was regarded humorously by the group as it had been a common experience to have been suspected of this disease. In response to this question, many answered: "Not yet!"

Eighty-three, or 59.2%, of the group of 140 had a definite past history of allergic disease. The remaining 40.8% were negative. The criteria used for judging a positive allergy history were those used by Vaughan[5] in determining the incidence of allergic manifestations in a sample population.

In the positive group of 83 cases, infantile or flexural dermatitis had occurred in 10 cases, asthma in 16, pollinosis or seasonal hay fever in 31, the probable diagnosis of perennial allergic rhinitis was made in an additional 30 cases. Of the latter group, it should be said that it is difficult to determine the presence or absence of an allergic rhinitis from the history alone; in these cases, particularly when seen at the time of nasal symptoms, the appearance of the nasal mucous membranes and the examination of the nasal secretions for eosinophils aided in making the diagnosis. A non-seasonal allergic rhinitis as judged by the history existed as the sole allergic manifestation in only 10 of the 30 cases; in the remainder one or more other allergic expressions had existed at some time in the past. Cases were encountered which obviously needed to be followed for months before a correct appraisal as to the presence or absence of an allergic rhinitis could be made. This type of follow-up was not attempted in this series. Doubtful cases were not included in the positive group.

Urticaria on repeated occasions or in prolonged attacks occurred in 27 individuals. A history of recurrent sick headaches was present in 22. Definite gastro-intestinal allergic symptoms occurred in 15. This diagnosis was suspected in several others, but in retrospect could not be substantiated and was not used as a criterion for placing a given case in the positive series. Frequent, recurrent canker sores occurred in 21 of the 83 positive cases, and in 9 of 57 with negative

histories. Five nurses of the positive group gave histories of serum sickness. No such cases were found in the negative group. The occurrence of either canker sores or serum sickness was not regarded as evidence for labeling a person an allergic individual. As might be expected, the majority of those in the positive group, 60 of 83 cases, had more than one allergic manifestation in their past history.

In response to the question: "Do you have periods of fatigue unrelieved by rest?", 43 (51.8%) of the positive group answered in the affirmative against 3 (5.3%) of the negative cases.

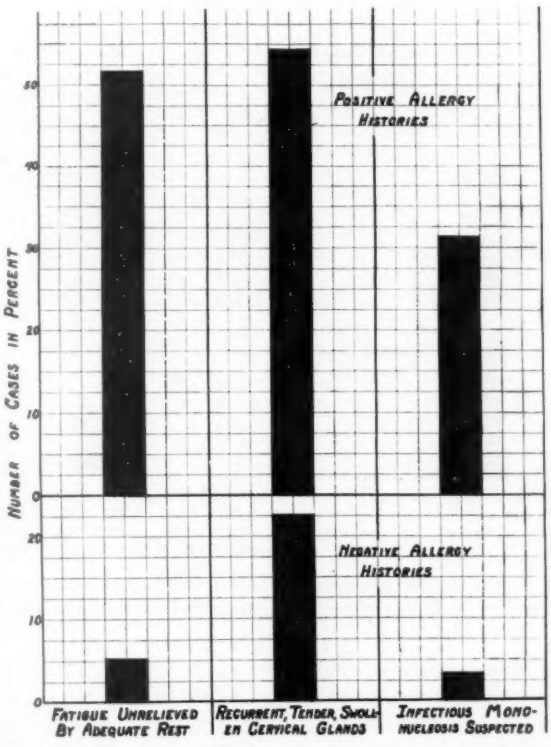
Positive Allergy Histories
Negative Allergy Histories
Number of Cases in Percent
Fatigue Unrelieved By Adequate Rest
Recurrent, Tender, Swollen Cervical Glands
Infectious Mononucleosis Suspected

FIG. 1.—Symptoms of unexplained fatigue, recurrent, tender, swollen cervical glands and the suspicion of infectious mononucleosis in relation to a history of allergic disease.

A past history of recurrent, tender swollen cervical glands was obtained in 44 (54.2%) of the positive group and in 13 (22.8%) of the negative cases. Within the positive series noticeable cervical gland involvement occurred only in association with upper respiratory infections in 12, both in association with and in the absence of upper respiratory infections in 17, and spontaneously or without reference to upper respiratory infections in 15. Of the cases with negative histories for allergy, 8 fell into the first group, 1 in the second, and 4 in the third. Of the latter 4, where cervical gland involvement had occurred, without relation to an upper respiratory infection, 1 case was diagnosed

as infectious mononucleosis, 1 noted swollen glands with each menstrual period, and 1 had noticed tender enlarged cervical glands intermittently since a preceding mastoid infection. (See Fig. 1.)

The majority of the individuals answering this question in the affirmative had been subject to repeated bouts of swollen glands, often dating back to childhood. The terms upper respiratory infection and the common cold were used synonymously. The characteristic features of this clinical entity were described in each case as the question was asked.

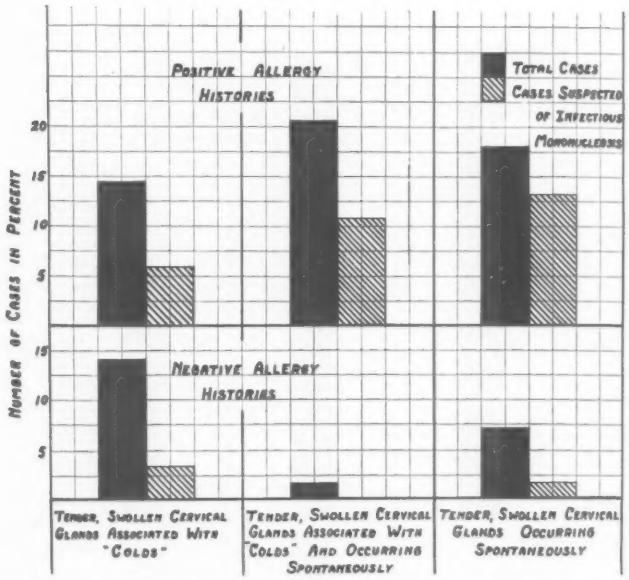

FIG. 2.—The relationship of a history of allergic disease to that of tender, enlarged cervical glands with or without upper respiratory infections and the suspicion of infectious mononucleosis.

Infectious mononucleosis had been suspected in 27 (31.5%) of the 83 cases with a positive allergy history against 2 (3.6%) of those with a negative history; it had been diagnosed on the basis of a positive heterophil antibody determination in 1 case of the former and in 1 of the 2 suspected cases in the latter group. Either the presence of an unexplained fatigue or the history or physical finding of a cervical adenitis had usually suggested the diagnosis. In a smaller number of cases the finding of atypical lymphocytes in the peripheral blood had suggested the possibility of infectious mononucleosis. The history of cervical adenopathy in relation to the suspicion of infectious mononucleosis is shown graphically in Figure 2. As one might expect, those cases having spontaneous or unexplained enlargement of the cervical glands were more commonly suspected of having glandular fever.

Of the 27 individuals having a past history of allergic disease and suspected of having infectious mononucleosis, seasonal or perennial allergic

rhinitis had occurred in 20, recurrent sick headaches in 9, urticaria in 8, bronchial asthma in 6, gastro-intestinal allergy in 6, and atopic dermatitis in 3.

At the time of recording the allergy history, a differential W.B.C. count (100 cells) was obtained. The number of atypical lymphocytes varied from 0 to 22% and bore no constant relationship to the presence or absence of a past history of allergic disease, an average of 5.5% was found in each group. It should be mentioned that the majority of patients with a positive past history of allergy were not having allergic manifestations at this particular time.

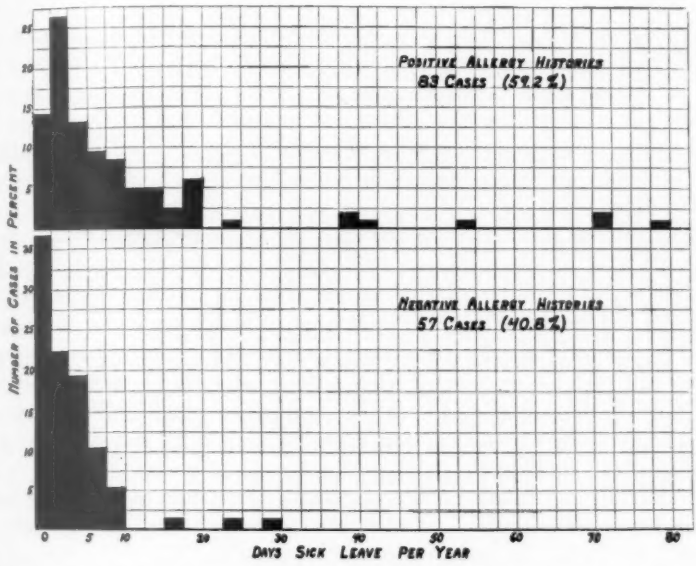
Positive Allergy Histories
83 Cases (59.2 %)
Negative Allergy Histories
57 Cases (40.8 %)
Number of Cases in Percent
Days Sick Leave Per Year

Fig. 3.—Days sick leave per year in relation to the past history of allergic disease.

In reviewing the medical records of this entire series of cases, we were impressed by the relative thickness of the files of the cases with positive histories of allergic disease in contrast to the negative group. It then seemed desirable to determine the amount of time lost per year in each case. Members of the Senior class were followed in this respect for 2 years, the Junior class for 1 year. The results of this survey are represented graphically in Figure 3. Those in the positive group lost on the average of 10.7 days, those in the negative group 3.5 days per year. One striking case in the former series was hospitalized 25 times in a period of 18 months because of undiagnosed allergic headaches. This case was correctly diagnosed later and the headaches were controlled by dietary management.[4] Several cases lost more than 20 days per year as a result of operations, fractures, or severe infections. When the cases of both series who lost more than 20 days per year are deducted, the average time lost by the positive group was 5.8 days against 2.6 days for those with negative past

histories of allergy. Those with no sick leave were more apt to have a negative history of allergy than a positive one.

Discussion. The finding of a positive past history of allergic disease in 59.2% of a group of 140 student nurses agrees with surveys conducted by others. Vaughan[10] studied a small community (508 persons) and found that 53.7% had a past history of allergic disease and a questionable history of allergy in an additional 9.8%. Pipes,[3] in a similar survey of 700 individuals of varying age, found an incidence of allergic disease in 44.4%.

To our knowledge, previous surveys have not been concerned with the question of fatigue or variations in the cervical glands in relation to the history of allergic disease.

It is a significant finding that periods of unexplained fatigue occurred in 51.8% of the cases with a positive allergy history, in contrast to 5.3% of those with negative histories. This fatigue, as observed clinically, is not relieved by the usual amount of sleep per night or by obtaining an excessive amount of rest. It is apt to be most marked in the morning, patients frequently volunteering the information that they are more tired upon arising than when they went to bed.

It is suggested that unexplained fatigue is a constitutional symptom of uncontrolled allergic disease, occurring most frequently in association with some definite allergic manifestation. Although frequently observed in cases of allergic intolerance to foods, it is by no means limited to the food allergic response. It is a typical symptom of serum sickness and often persists for weeks after all other evidence of this manifestation has subsided. It is sometimes observed in cases of seasonal hay fever; in occasional cases it may be a more distressing symptom than the rhinitis.

Clinically it is similar to the lassitude occurring in influenza and infectious mononucleosis, in both instances the fatigue may persist for many weeks as the only residual symptom.

The past history of recurrent, swollen cervical glands in 54.2% of the group with positive histories, against 22.2% with negative histories, is also statistically significant. Swollen glands occurring only in association with upper respiratory infections, were present in approximately the same incidence in both the positive and negative series. However, there was a marked difference between the two groups in the incidence of spontaneous attacks of swollen cervical glands. These cases comprise the second and third groups of Figure 2; a past history of allergic disease was the rule, and many of these cases had been suspected of infectious mononucleosis.

The majority of the cases giving a history of tender swollen glands at some time in the past had normal peripheral glands upon physical examination on the date of their history and blood count. A few cases happened to be seen during the course of an upper respiratory infection, some of these were found to have tender and enlarged cervical glands, and a few had a significant number of atypical lymphocytes in the peripheral blood. This response of the blood in the course of an upper respiratory infection has been observed by others.[1,9,11]

A small group happened to have acute allergic symptoms at the time these studies were undertaken. The blood findings in a few of these cases were similar to those previously reported.[5] One patient was seen in consultation 3 months prior to the date of the survey. She complained of a persistent fatigue and rhinitis of 2 months' duration. Differential blood studies revealed 24% of atypical lymphocytes. Another determination 2 days later revealed 12%. She had been hospitalized on 1 occasion 6 months earlier because of unexplained fatigue. While in the hospital, she developed tender and slightly enlarged cervical lymph nodes and a palpable spleen, although her heterophil antibody response was negative. At no time was there evidence of infection to explain these findings. On various occasions she was observed to have an eosinophilia between 5 and 8%. At the time of her survey blood count, she was symptom-free, her lymph glands were normal on examination, and she had only 2% of atypical mononuclear cells in the blood.

The fact that a single blood count failed to show any significant difference in the number of atypical lymphocytes as seen in the positive and negative groups is not surprising. In the first place, the method available for studying the lymphocytes, that is, differential counts from stained film preparations, affords data that is more qualitative than quantitative. Inaccuracies in the enumeration of large cells from either the cover-slip or slide preparations are well known. Repeated determinations in a given case have shown considerable variation in the number of abnormal appearing lymphocytes. In spite of this uncontrollable error in the enumeration of these cells, there is reason to believe that the number of such cells varies from time to time and is apparently dependent upon the presence of lymphoid hyperplasia some place in the body as pointed out by Baldridge, Rohner and Hansmann.[1]

Lymphoid hyperplasia may, in turn, be the result of bacterial antigenic stimulation, such as may occur during the course of an acute upper respiratory infection, or it may be associated with non-bacterial antigenic stimulation as, for instance, in the person sensitized to foods or serum. Rich[6] has emphasized the latter mechanism as a cause of experimentally induced lymphoid hyperplasia in animals.

Clinically there is considerable evidence that, at least in younger individuals, the lymphoid tissue participates in the allergic response. At times of allergic symptoms, examination of these individuals commonly reveals evidence of enlarged peripheral glands; enlarged, edematous tonsils or hypertrophied masses of lymphoid tissue in the posterior pharynx. How frequently the hidden lymphoid tissue of the body, such as that in the gastro-intestinal tract for instance, may participate in the reaction remains speculative. Evidence in support of the concept that the lymphoid tissue participates in the allergic reaction will be presented in detail in another article.

Summary. A survey of 140 student nurses showed that 59.2% had a positive past history of allergic disease.

The complaint of "fatigue unrelieved by adequate rest," and the

history of intermittent, "spontaneous" enlargement of the cervical lymph nodes, occurred much more commonly in those with a past history of allergic disease than in the negative controls. This resulted in a diagnosis of infectious mononucleosis being suspected in 31.5% of those with an allergic background, as against 3.6% of those with a negative past history of allergy. Infectious mononucleosis was diagnosed on the basis of a positive heterophil antibody determination in 1 case of each group.

The average number of days sick leave per year in the group with positive allergy histories was over twice that occurring in the group with negative allergy histories.

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THE USE OF BROMSALIZOL IN LENGTHENING THE EFFECT OF A SYMPATHETIC NERVE BLOCK*

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In a recent preliminary communication,[4] it was pointed out that mono-brom-hydroxy-benzyl alcohol, more familiarly known as bromsalizol, would block conduction in sympathetic nerve trunks for as long as 8 consecutive days after a single injection. The chemical and pharmacologic properties as well as some of the clinical applications of this drug were described fully in 1934[5] and it need only be mentioned here that its 3 outstanding characteristics are: (*a*) anesthetic, (*b*)

* All the bromsalizol used in this report was kindly supplied by Hynson, Westcott and Dunning, Inc.

antispasmodic, and (*c*) low toxicity. Because of its low solubility in water, peanut oil was used for a vehicle; a 4% solution of bromsalizol in peanut oil, furnished in 10 cc. glass ampoules, was the standard preparation used for all the observations in this report.

Technique. The technique of giving a paravertebral block has been described frequently. The method used for this report was as follows:

Premedication consisted of morphia sulphate 12 mg. ½ hour before the lumbar paravertebral block was to be given; for the stellate ganglion block, sodium luminal 128 mg. and atropine sulphate 0.6 mg. were substituted for the morphia in order to avoid the small pupil in the test for Horner's syndrome. Atropine was given to avoid a vagal cardiac reflex.

For the lumbar block the patient was placed on his side, the spine of the second lumbar vertebra marked with ink. After skin preparation and draping, a point 4 cm. lateral to the spine and opposite to the side on which the patient was lying was infiltrated with 0.5% procaine, using a fine needle, the anesthetic being then continued to the transverse process where 5 cc. of procaine were placed. A small folded piece of rubber was then pierced with the No. 19 gauge paravertebral needle which was inserted down to the transverse process. The rubber marker was then adjusted so that it was 4 cm. from the skin. With a 10 cc. syringe, containing 0.5% procaine, attached, the needle was lifted well off the transverse process, and directed medially either below or preferably above the process, infiltrating as it advanced toward the body of the vertebra. Once the vertebra was reached, the needle was moved up along it until the anterior psoas fascia was pierced at the vertebra. Ordinarily the rubber marker on the needle would be touching the skin at this point, and when this position was reached 10 cc. of 0.5% procaine were injected followed by one 10 cc. ampoule of bromsalizol. There should be a sudden release or "give" of the needle as it passes over anterior lateral edge of the vertebra. The same procedure was then carried out for the next lower interspace. Only rarely were 3 lumbar segments injected.

In case of the stellate ganglion block, with the patient seated on a stool, 4 cm. were marked off lateral to the vertebra prominens, and at this point a procaine 0.5% injection was carried down to the first rib. The rubber marker was then set at 3 cm. and the needle was directed below the rib and sharply medially along the body of the vertebra until the rubber marker had touched the skin, infiltration taking place constantly as the needle point progressed. Frequent aspirations were necessary to test whether the pleura had been punctured. Once the needle point had reached the desired depth, 10 cc. of 0.5% procaine followed by a 10 cc. ampoule of bromsalizol were injected.

To avoid the possibility of placing oil in the blood-vessels, it was important that repeated aspiration showed no return of blood before the bromsalizol was injected. If bleeding occurred, a small local readjustment of the point of the needle was usually all that was necessary; however, it was occasionally necessary to abandon injection of a particular segment because of hemorrhage.

There are many variations of the above technique. Many physicians avoid the use of a syringe in placing the needle, thus getting a greater delicacy of touch, but sacrificing the benefit of immediate infiltration and aspiration.

Contraindications for the test are a sensitivity to procaine or bromsalizol. So far no routine sensitivity tests have been made before injection. Only 1 case exhibited sensitivity by having generalized dermatitis and hyperpyrexia. This individual later was found to be equally sensitive to peanut oil, as well as to bromsalizol oil by skin tests.

With the above technique, the extremity showed an increased skin temperature by the end of 30 minutes; if bromsalizol alone was used, this effect might not take place for 3 to 7 hours. It was not uncommon for the skin temperature to drop 48 hours after the injection and then to rise again (Fig. 1). Ordinarily in old arteriosclerotic patients the lower extremity would stay warm for 5 consecutive days and gradually get back to normal by the end of the 8th day. However, there were many variations. In patients between 35 and 45 years of age, the effect might last only 3 days. Occasionally there would be an immediate effect lasting a few hours, and then an interval of 1 or 2 days might follow with only intermittent signs of a block, to be supplanted finally by the usual signs which showed that the block had taken effect.

For all practical purposes, simple palpation showed whether the injected side was warm and drier than the opposite side. Inspection of the sole of the foot found this to be redder than its counterpart. Occasionally, skin temperatures were taken with the aid of a thermocouple (Figs. 1 and 2); a few skin resistance determinations were also made. Subjectively, a feeling of warmth throughout the extremity and cessation of pain were frequently mentioned by the patients.

In older individuals, particularly those that have marked arteriosclerosis and are thin, the effect may last 10 days. The longest interval so far observed is in a 70 year old diabetic in whom the first block lasted 6 days, and the second block done over 4 months ago, still shows at this writing a warmer leg on the injected side as determined by the dermatherm, and a block as complete as sympathectomy as established by electric skin resistance measurements. In this patient it is possible that the lumbar sympathetic chain or one or more ganglia were directly infiltrated and possibly damaged by the injection.

Much of the variation in the lumbar blocks may be explained on the accuracy with which the oily bromsalizol is brought in contact with the sympathetic nerve trunk. In obese individuals a thin layer of fat separating the bromsalizol from the chain might explain a poor reaction, even though the aqueous procaine solution had penetrated the fatty tissue more readily, and given an early satisfactory response. In addition, it is known anatomically that there is much variation not only in the number, location and distribution of the ganglia in the lumbar sympathetic chain, but also in the constitution and location of the chain itself.

In all the cases of stellate ganglion block, the results have been better than for the lower extremity. The shortest interval of a dry, warm hand was 17 days; the longest, as vouched for by a letter from the patient, was 1 month.

In a total of 103 patients, there have been 5 failures, probably due to faulty technique. Two were in old men with extensive osteoarthritis of the spine, which increased the difficulty of placing the needle. For the other 3 we have no explanation; possibly the needle was not inserted far enough.

In no case was the use of bromsalizol followed by symptoms of severe peripheral neuritis which not infrequently follows paravertebral

alcohol injections. However, 2 patients complained of a mild burning pain in the groin which disappeared completely in 2 weeks.

To date only 1 patient, a woman of 67 years with diabetic gangrene and osteomyelitis of the tarsal bones, has received as much as 4 paravertebral lumbar blocks. Each subsequent injection had the general effect of the initial block which lasted 9 days. This result has been generally characteristic of all repeat injections.

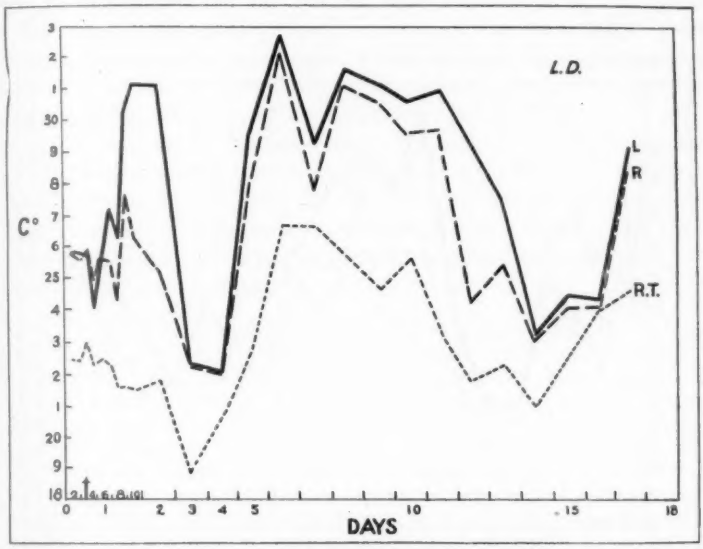

FIG. 1.—The difference in temperature following a left lumbar paravertebral block with 20 cc. of bromsalizol alone. Dermatherm temperature readings were taken from the skin of the plantar surface of the big toe. It will be seen that it took 4 hours before the left big toe became warmer than the right. The subsequent great difference in temperature occurred on the following day, but did not persist. However, another marked difference occurred on the 12th day. There was no consistent great difference in temperature readings. *L.*, left big toe; *R.*, right big toe; *R.T.*, room temperature; the arrow marks the time of the block. All the values were corrected to 29° C. for the constant thermacouple, and to 21° C. for the room temperature.

In this connection it may be mentioned that sympathetic ganglionectomy performed 1 week after a single paravertebral block with bromsalizol showed that the tissue along the chain was mildly inflamed and friable; bleeding was slightly increased. A lumbar ganglionectomy was performed on the patient mentioned immediately above who had 4 paravertebral blocks, and in this instance, the tissues along the chain were extremely friable and suggested the presence of a sterile subacute inflammation.

To rule out the possibility that the results could have been attributable to the procaine and not to the bromsalizol, it is only necessary to say that the first 20 cases were injected with bromsalizol alone and they showed the typical results as mentioned above. In addition the following 2 curves of thermocouple skin temperature readings are given to show that when bromsalizol alone was used, the effect was

essentially the same as when procaine was added to the bromsalizol (Figs. 1 and 2). The chief difference between these 2 curves is the early temporary rise in temperature with the procaine.

Bromsalizol has been used not only for diagnostic purposes in determining collateral circulation and pathways of pain, but also for its therapeutic value. Among the types of cases that were benefited by the injections, the following may be mentioned. But since only relatively few patients have been treated, final evaluation must depend on more cases.

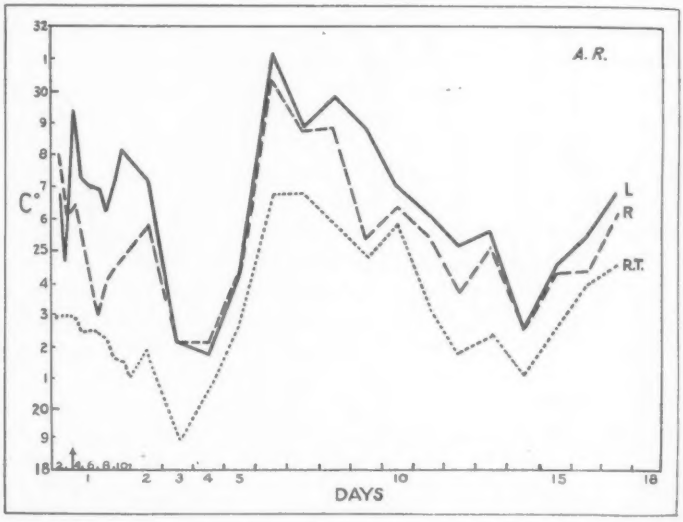

FIG. 2.—The same as Figure 1 except that the paravertebral block was done with 20 cc. of bromsalizol in addition to 20 cc. of 1% procaine. Because of the procaine a prompt difference in temperature was recorded at once. Both patients, L. D. and A. R., were controls, studied at the same time and under the same conditions. L. D., BCH. 81019, a white male, 73 years old, had a fracture of the right tibia; A. R., BCH 86231, a white male, 67 years old, had a right intratrochanteric fracture.

1. *Bromsalizol has been of great benefit consistently in acute thrombophlebitis.*

CASE 1. A. M., a white female, age 17, BCH 87219, was admitted to the medical service on March 31, 1944 with a 3 weeks history of right chest pain, fever, increasing shortness of breath, and cough productive of grossly bloody sputum. The physical findings on admission were compatible with a diagnosis of extensive pneumonic involvement of the right middle and lower lobes, and the left lower lobe of the lungs. Digitalization and oxygen therapy were necessary because of toxic myocarditis with decompensation. She was given sulfadiazine, 6 gm. daily by mouth, with poor response, the temperature ranging between 103° to 104.8° F. the 1st week, and between 100° and 102° F. the 2nd week. The sputum and chest pain disappeared about the 12th hospital day, and the patient was clinically improved. Digitalis and sulfadiazine were stopped during her 3rd hospital week. On the 20th hospital day she complained of pain in the right thigh, and a diagnosis of thrombophlebitis of the deep femoral vein in the upper right thigh was made. Her temperature during the 3rd week ranged between 100° and 101° F. Paravertberal block was performed on the 21st hospital day with novocain and bromsalizol. The symp-

toms rapidly subsided with immediate disappearance of pain which had been excruciating. The tenderness, which was severe, disappeared after 3 days and the edema was only slight after 4 days. The patient's temperature rapidly fell to normal on the 27th hospital day and remained so. Tenderness returned on the 29th hospital day and the patient received a paravertebral block of bromsalizol on the following day. The tenderness disappeared within 24 hours, and the patient was clinically well except for a very slight persistent edema. She was up walking about the ward on the 36th hospital day, and was discharged, walking, May 12, 1944.

In the other cases, only a single injection was necessary, with the exception of 1 patient who required a second injection 9 days later. This use of bromsalizol is in sharp contrast to the more frequent blocks with procaine as advocated by Ochsner and DeBakey.[6] Veal and Hussey[7] even suggested blocks every 12 hours in the acute phase.

2. *Postphlebitic edema following recent thrombophlebitis.* Bromsalizol has been of particular benefit in this group of cases which ordinarily has been treated by compression bandage and elevation of the leg, and only too frequently with indifferent success as evidenced by the enlarged, painful, cold extremity.

CASE 2. A. K., a white female, age 25, was referred by Dr. G. B. Jastram, of Aberdeen, Md., for treatment of bilateral femoral postphlebitic edema. The acute phlebitis involved the left leg from December 16 to December 23, 1943, and the right leg from December 24, 1943, to January 10, 1944. She presented the following symptoms when given the paravertebral block of bromsalizol and novocain on January 30, 1944. There was marked edema of the feet and legs which was less on the left. There was moderate tenderness of the legs and feet which were also cool, moist, and cyanotic. Both legs became warm and dry in 24 hours. The left leg remained so for 10 days, and the right leg for 14 days when sweating of normal character returned. The color of the legs and feet returned to normal in 48 hours and remained so. The tenderness disappeared completely in the left leg and foot in 2 days, and in the right in 4 days, except for very slight tenderness of the right instep. The edema declined rapidly in both legs, and disappeared completely in the left leg and foot after 2 weeks. The edema disappeared from the right leg and foot except for slight swelling of the instep after exercise at the end of 2 weeks. On examination on March 9, 1944, 39 days after injection, after the patient had been on her feet doing housework all day with no elastic support of the extremities, the following was found: The extremities were normal in color, free of tenderness, perspiring normally, and free of edema except for very slight swelling of the right instep.

This paravertebral block was an office procedure; the patient returned home in 1 hour, and assumed her routine duties of housewife in 24 hours. The patient illustrates furthermore the possible economic benefits to be derived from this form of treatment.

In another case, an equally successful result was obtained in a patient who had had edema of a leg 2 months after the acute phase had subsided.

3. *Simple arteriosclerosis has been helped primarily in the healing of ulceration.* In the case of a 73 year old colored man who had had 2 toes amputated at another hospital several weeks prior to admission, and whose ulcer at the operative site had shown no tendency to heal, there was progressive and eventually complete healing after 2 bromsalizol blocks. He was discharged walking on his healed foot.

The symptom of intermittent claudication in arteriosclerotic patients has also been relieved for 10 consecutive days in 3 patients after a single injection.

4. *Arteriosclerosis complicated by diabetes.* This group comprises 3 cases, all of whom were far advanced in the healing stage, and none required amputation. The following case illustrates this group.

CASE 3. J. S., a white male, age 70, BCH 87744, was admitted to the Baltimore City Hospitals December 30, 1943, with a diabetic ulcer in a large callus over the head of the second metatarsal of the right foot, and a cellulitis extending to the knee. A posterior tibial artery pulsation was present but the dorsalis pedis artery was not palpable. A paravertebral block with bromsalizol and novocain was given on December 30, 1943, and the leg was placed in warm moist compresses. On the following day the sole of the foot was incised through the callus and a large pocket of infected gangrenous tissue opened. Three days later, because drainage was inadequate and the second toe had become obviously gangrenous, a second operation was performed in which the second toe was disarticulated and the plantar incision was carried toward the heel until good tissue was reached. Compresses were discontinued on January 4, 1944. The paravertebral block was repeated with bromsalizol and novocain on January 5, 1944. His temperature ranged between 99.8° and 101° F. for 4 days, then gradually fell to normal on the 7th hospital day, and except for occasional slight elevations, remained there throughout his hospital stay. The right leg stayed continually warmer than the left, and it was not necessary to repeat the paravertebral block after the second one. The necrotic tissue gradually sloughed with the use of azochloramide irrigations and compresses, and the area of incision healed except for a small draining sinus beneath the second and third metatarsal heads which appeared to be coming from the infected flexor tendon of the third toe. The patient was discharged walking on February 23, 1944, and worked as a drug clerk from 5 to 7 hours daily, being dressed at weekly intervals in the Out-Patient Department. The sinus persisted, and Roentgen ray picture on April 25, 1944 revealed involvement of the metatarsophalangeal joint of the third toe. The patient was readmitted to the hospital on May 2, 1944 and on May 4 the third toe and distal one-half of the third metatarsal bone were excised under spinal pontocaine anesthesia. Following this, the wound healed rapidly and the patient was discharged walking on May 12, 1944 with the wound well healed. The right leg was tested against the left with the dermatherm and found to be much warmer, indicating a persistence of effect of the last paravertebral block on January 5, 1944. The patient stated that he had noticed that the right leg had been continually warmer than the left. Skin resistance measurements were made on May 12, 1944; they confirmed the dermatherm readings and indicated a complete sympathetic block with some spread to the left buttock.

Because of the success of the bromsalizol blocks, the patient has so far been spared a lumbar sympathetic ganglionectomy and possibly a major amputation.

5. *Bromsalizol has been helpful in cellulitis in the feet of arteriosclerotic patients.* It has also aided in limiting the area of gangrene and speeding the process of demarcation.

6. *Bromsalizol has been helpful in healing amputation stumps.* In the case of a Negro 82 years old with gangrene of the toes of the right foot, a Symes amputation of the foot after a bromsalizol lumbar sympathetic block was attempted. Healing almost succeeded. However, an amputation below the knee was performed later; the incision over the fibula broke down but healing eventually occurred after

repeated bromsalizol blocks. In another case, amputation of the second toe for an indolent arteriosclerotic ulcer at the first interphalangeal joint was followed by healing after a bromsalizol block. In 2 cases, healing of the stump in a supracondylar amputation after lumbar sympathetic blocks seemed to take place more quickly than usual.

7. *Two cases of frostbite were treated by bromsalizol blocks.* In 1 patient, a 33 year old colored male, who had bilateral frostbite and gangrene of the tips of all toes, with the right foot worse than the left, received one lumbar bromsalizol block on the right side. The left side was not blocked, and was used as a control. Healing on the right side was faster than the left even though this side was more severely damaged originally. Eventually only the tips of the toes of both feet were lost.

8. *Thrombo-angiitis obliterans.* Only 1 case was seen.

CASE 4. I. M., Johns Hopkins Hospital, No. 318984, a 35 year old, active, non-smoking Jewish business man was referred by Dr. Lay Martin, Baltimore, Md., with symptoms of moderate intermittent claudication in both legs, worse on the left. Immediately after the bromsalizol block on the left side, symptoms came on as before when he walked, but the pain subsided more quickly. On each of the two following days he walked a mile with the usual discomfort on the right side but none on the left. A report received 5 weeks later showed that he still had some benefit from the block. Whether repeated blocks will let him escape lumbar sympathectomy is still problematical.

9. *Arterial occlusion.* In 2 cases of femoral arterial embolism, a single lumbar block with bromsalizol gave complete relief from pain for 13 days in 1 case and only moderate relief in the other instance. Two cases of arterial thrombosis were treated with similar results. There were also single instances of venous clinical pictures which were treated.

The following single instances are worth recording.:

10. *Angina pectoris.* A patient, F. P., 49 years old, referred by Dr. N. B. Herman, Baltimore, Md., with symptoms of angina pectoris, and with myocardial damage as shown by the electrocardiogram, received a bilateral block of the stellate ganglia with bromsalizol; bilateral enophthalmus was present for 2 days, the right hand remaining warm and dry for 17 days and the left hand for 30 days.

Obviously nothing can be claimed for bromsalizol in this instance even though 4 weeks later he could walk a half a mile in reasonable comfort after having been virtually bed-ridden before. Even though the function of the sympathetic nerves with reference to the coronary arteries is still not firmly established,[1,3] the possibility exists that useful information may be obtained from these paravertebral blocks.

11. *Dermatitis.* A case of infected atrophic eczema of both legs seen in consultation with Dr. J. Ralph Horky, Churchville, Md., was treated by a bilateral bromsalizol block. The infection immediately subsided, and improvement was sustained for 1 month when another block was given with equally good results.

12. *Obstetrics.* To relieve the pain in childbirth the method of Jarvis,[2] who used frequent paravertebral blocks of procaine, was supplemented by the addition of bromsalizol. The results so far have

not been clear-cut enough to report, but the indications are that much of the pain in the first stage of labor can be relieved by a single injection.

13. *Unexplained pain.* In a man of 59 years, with bilateral unexplained stabbing pains in the calf, sole, and toes of both legs, worse on the right, a bromsalizol block was given first in the right side. He obtained such marked relief that he insisted on a block for the other side. He has not had a return of pain to date, namely, 4 months after the initial block.

Stated simply, bromsalizol does no more than the ordinary procaine paravertebral block except that the effect is longer, even though the intensity is not as great (Figs. 1 and 2). However, there is the possibility that in certain fortunate injections like the 2 mentioned above in which the effect was still present 4 months later, that the needle point actually damaged the sympathetic trunk. Only further observations will be able to establish how long such a block will remain, but for the present it can be stated that a bromsalizol block seems to have accomplished for 4 consecutive months as much as could have been expected from a lumbar sympathetic ganglionectomy.

It is possible that bromsalizol may be of value in two large groups of cases. In the first instance, by preventing vasoconstriction and thus providing better circulation, the drug might improve any inflammatory process anywhere in the body. In injuries of the extremities in war and industry, when prolonged relief of vasospasm may save the extremity, bromsalizol may have its place. In the second instance, by blocking the pathway of pain along the sympathetic trunk, it might bring relief to cases of dysmenorrhea, causalgia, or inoperable malignant tumors. Any condition which has not been benefited by sympathetic ganglionectomy would probably not be helped by bromsalizol.

In general, the entire field of peripheral anesthesia so far has been limited essentially to its two extremes—either a short temporary phase, or a permanent nerve paralysis. Apparently there is no intermediate interval between the anesthesia of a few hours as given by a host of substances, and the permanent loss of conduction by destroying the continuity of a nerve either by the scalpel or alcohol injection. An exception may be made in the case of the proctologists who have tried many drugs and chemicals, such as quinine and urea, to bring relief for longer periods in such conditions as pruritus ani. What is badly needed is an anesthetic which is operative for days and possibly months. Bromsalizol may prove to be an entering wedge. It apparently has no paralyzing effect on the human peripheral somatic nerve, because in 2 patients the ulnar nerve at the elbow was bathed in 10 cc. of the preparation without any sign of an ulnar nerve paralysis.

Experimentally, the effect of bromsalizol on the peripheral sympathetic system of dogs showed an entirely different reaction than had been expected. In 2 dogs, the vagus nerve, which carries with it the cervical sympathetic trunk in the neck, was freed widely from the common carotid artery under surgical conditions. The wound was filled with 5 cc. of bromsalizol which completely surrounded and bathed the nerve. However, no constricted pupil as a sign of Horner's syn-

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drome appeared. In 4 instances, the chest was opened aseptically in the second interspace, and 5 cc. of bromsalizol was injected in the region of the stellate ganglion. Again no Horner's sign was seen. In a 5th case, the sign did appear within 12 hours and has persisted for 20 days. In a 6th dog, 10 cc. of bromsalizol was injected, and also no Horner's sign was obtained. Whether the needle point damaged the stellate ganglion in the 1 case in which a small pupil resulted, cannot be determined at present. In 2 more animals the chest was opened under sterile precautions, and the stellate ganglion was freely exposed after stripping away the pleura. Ten cc. of bromsalizol were then injected all around the ganglion. Again there was no evidence of Horner's sign. At all events, it seems as if bromsalizol affects the human but not the canine peripheral sympathetic system. The reasons for this difference are open to investigation.

Furthermore, the marked difference in effect as between man and the experimental animal naturally brings up the question as to the extent to which it is justifiable to expect similar reactions in the two groups. It may well be that certain drugs and chemicals may have a profound effect on man without affecting the experimental animal. On this basis alone, many substances anesthetic to man may have been discarded because they had no effect on the experimental animal.

Summary. A 4% solution of mono-brom-hydroxy-benzyl alcohol (bromsalizol) in peanut oil was used for paravertebral blocks of the sympathetic nerve trunks of 103 patients.

It was found that the blocks with this drug gave a much longer beneficial effect than with the usual procaine. In old arteriosclerotic patients the effect of a lumbar block would last for 5 consecutive days and then gradually disappear by the 8th day. In 2 cases, the block was still effective after more than 4 months. In younger patients the effect might last only 48 hours. In 5 cases no effect was obtained.

The stellate ganglion block in the 4 available instances lasted from 17 to 30 days. It was much better than the lumbar block.

The best results were obtained in cases of femoral thrombophlebitis; a single injection was usually sufficient for the acute phase, and in 2 cases treated immediately after the acute stage, a single injection was enough to reduce the swelling almost entirely.

By improving the circulation, bromsalizol has been successfully used therapeutically in cases of diabetic ulcers and gangrene, in cellulitis of the foot, in frost-bite, in amputations below the knee, in temporarily relieving the pain of intermittent claudication in arteriosclerosis and thrombo-angiitis obliterans, in arterial vasospasm, and in temporary relief from dermatitis.

Bromsalizol has been used diagnostically as a clinical test for collateral circulation.

Bromsalizol was injected around the ulnar nerve without causing any signs of nerve paralysis.

In dogs, bromsalizol did not produce a Horner's syndrome when injected around the stellate ganglion.

It is a pleasure to make the following acknowledgments. The facilities for the animal experimentation in the Surgical Hunterian Laboratory were extended by Dr. Alfred Blalock, Professor of Surgery at the Johns Hopkins Medical School; the dermatherm was loaned by Dr. Arthur M. Shipley, Professor of Surgery at the University of Maryland; the skin resistance measurements were made by Mrs. Woodruff and Miss Evans of Dr. Curt P. Richter's Psychobiological Laboratory, Johns Hopkins Hospital.

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SPERMATOGENIC ACTIVITY OF VARIOUS STEROIDS*

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Numerous experiments[3,6,9,10,15] have shown that testoid substances, as well as anterior pituitary gonadotropins, inhibit testicular atrophy in hypophysectomized rats. More recently, Albert and Selye[2] and Selye and Friedman[13] reported that steroids devoid of testoid potency such as Δ^5-pregnenolone and progesterone exhibit spermatogenic activity. These conclusions were confirmed with Δ^5-pregnenolone by Ruzicka[11] and Leathem and Brent.[5] The latter showed furthermore that ethynyl-testosterone, which like progesterone produces marked progestational changes in the rabbit, is completely inactive in this respect.

At first Nelson and Merckel[10] claimed that male hormone preparations as well as testoids were unable to reinitiate spermatogenesis in adult rats which had been hypophysectomized for several weeks. However, in subsequent publications[7,8] they rectified their statement, indicating that if an adequate dosage is given, sperm formation is restored even if the treatment be started 22 to 28 days after the operation. Similarly, Cutuly *et al.*[3,4] found that spermatozoa may occur in the seminiferous tubules of immature hypophysectomized rats treated with testosterone propionate and "dehydroandrosterone acetate."

Unfortunately some of these data are not of great value for comparative purposes because the authors used either impure urinary

* The expenses of these experiments have been defrayed by a grant from the Gelatin Products Company, Detroit.

extracts or insufficiently described compounds. Since only common names such as androstenediol (trans) or dehydroandrosterone were mentioned, and no melting points given, it is difficult to determine the exact nature and the degree of purity of these preparations.

In the present paper we wish to report on a series of investigations in which 16 steroids were tested under identical conditions in hypophysectomized animals.

Methods. All our experiments were performed on immature male albino rats weighing 40 to 60 gm. (average 50 gm.) at the onset of the experiment. They received the compounds to be tested in 0.1 cc. of oil subcutaneously twice daily for a period of 10 days, injections being started the day following hypophysectomy. All the steroids were given in the dose of 2 mg. per day, except for Δ^5-pregnenolone, which was assayed at 2-dose levels: 2 mg. and 1 mg. A diet consisting mainly of "Pablum"* mixed with milk was found to be very satisfactory to maintain the animals in good condition. On the 11th day the rats were weighed and autopsied; the genital organs were removed and fixed in Suza for subsequent weighing and histologic study. Two criteria were taken for spermatogenic activity: the testis weight and the presence of spermatozoa in the seminiferous tubules. To ascertain the completeness of hypophysectomy, the following points were considered: absence of pituitary remnants visible with magnifying glasses, a body weight increase of less than 10 gm., adrenal weight of less than 10 mg., and atrophy of the accessory sex organs in the case of steroids known to be inactive as testoids.

Three groups of animals were taken as controls: the animals of Group 1 were non-operated and sacrificed at the beginning of the experiment; those of Group 2 were non-operated and kept for a period of 10 days; and finally those of Group 3 were hypophysectomized and treated for 10 days with cholesterol, substance devoid of any pharmacologic activity.

Results (Table 1). The steroids are arranged according to decreasing testicular weight. It will be noted that the testis weight of animals treated with active compounds is more nearly comparable to that of control Group 1 than of control Group 2. Therefore, none of the steroids so far studied is able to promote a normal growth of the gonads in the absence of the pituitary. On the other hand, the results of the histologic study show that spermatozoa are present in some experimental groups and control Group 2, while none could be detected in control Group 1. It seems evident that no relationship necessarily exists between the weight of the testis and the activity of the germinal epithelium. This is also substantiated by the fact that, in experimental groups having approximately the same average testis weight, some showed spermatozoa in more than one-half of the animals (androstenediol dipropionate and methyl androstenediol), while the others were negative (methyl testosterone and testosterone). In the case of the latter compounds there was, however, evidence of stimulation. Contrary to our findings, Cutuly *et al.*[3,4] reported that testosterone propionate induces sperm formation; a very likely explanation is a longer duration of treatment and the use of an ester instead of the free compound.

Selye[12] considered the prospermatogenic effect of the steroids as an independent pharmacologic activity. The present experiments confirm this conclusion. Although most of the active steroids stimulate

* Prepared by Mead Johnson & Co., of Canada, Ltd.

the accessory sex organs, as can be seen in the weights of the seminal vesicles and prostate, there is however no direct relationship between the testoid and the spermatogenic activity: androstenediol and its dipropionate, and Δ^5-pregnenolone have a very marked effect on the testis, although their testoid activity is moderate or *nil*. The spermatogenic activity is not subordinate to the luteoid activity: progesterone, methyl androstenediol, desoxycorticosterone acetate and ethynyl testosterone possess a strong progestational effect,[14] but the first 2 are active and the last 2 inactive on the testis. Obviously it is not subordinate to the folliculoid or corticoid activity.

TABLE 1.—EFFECTS OF VARIOUS STEROIDS ON THE TESTIS, PROSTATE AND SEMINAL VESICLES OF HYPOPHYSECTOMIZED IMMATURE RATS

Name of compound	M. p. (°C.)	No. of rats	Testis (mg.)	Seminal vesicles (mg.)	Prostate (mg.)	Spermatozoa*
Δ^5-androstene-3(β),17(α)-diol dipropionate	119–120	7	381 (183–495)	25.1 (17.5–34)	63.8 (50.6–102)	+(5) 0(2)
17-methyl-Δ^5-androstene-3(β),17(α)-diol	203–204	5	378 (310–449)	152 (123–179)	157 (129–184)	+(4) 0(1)
17-methyl-testosterone	164.5	7	364 (190–490)	165 (153–190)	156 (135–163)	0
17-methyl-androstane-3(β),17(α)-diol	211–213	6	329 (268–480)	153 (132–188)	159 (130–201)	+(1) 0(5
Δ^5-androstene-3(β),17(α)-diol	182–183	14	321 (195–490)	83 (62–103)	112 (96–145)	+(2) 0(12)
Testosterone	152–153	7	310 (210–420)	143 (80–190)	187 (136–275)	0
Δ^5-pregnenolone†	187–189	9	292 (138–458)	4.1 (3–6.7)	27.6 (22–37)	+(3) ±(1) 0(6)
Δ^5-pregnenolone‡	187–189	8	241 (82–418)	3.6 (2.3–6)	16.9 (7.6–26)	0
Progesterone	129	6	260 (180–380)	5.3 (3–9)	42 (32–77)	0
Δ^4-androstenedione	168–169	6	253 (130–308)	46.8 (32–73.4)	104.8 (45.7–160)	0(6)
Dehydroisoandrosterone	146	9	222 (96–310)	5.7 (4–10)	36.4 (17–53)	+(2) 0(7)
Ethynyl testosterone	265–267	11	116 (84–160)	24.1 (14–64)	43.3 (22–81)	0(11)
Desoxycorticosterone acetate	154–155	10	113 (76–180)	3.9 (2.6–6)	17.8 (9–19)	0(10)
Acetoxypregnenolone	182–183	7	109 (78–194)	2.7 (2.4–3.6)	11.4 (6.3–15.4)	0(7)
Cholesterol	149	11	105 (73–128)	3.7 (3.3–5)	10.2 (6–13.6)	0(11)
Control group I	...	10	306 (193–430)	5.1 (3.3–7)	29 (16.4–43)	0(10)
Control group II	...	10	878 (725–1170)	10.9 (8–16)	57 (42–69)	+(10)

Results of histologic examination to determine presence of spermatozoa are indicated by the following symbols: * + positive, ± doubtful, 0 negative. The numbers in brackets refer to the number of animals in the case of various responses within the same group.

† 2 mg. per day.

‡ 1 mg. per day.

It is interesting to note that Albert and Selye,[1] from their studies on the gonad-protecting activity of steroids against atrophy caused by estradiol, obtained results identical to our own. Evidently any steroid possessing spermatogenic activity is able to inhibit the testis atrophy resulting from hypophysectomy or treatment with folliculoids.

Summary and Conclusions. The spermatogenic activity of 16 steroids was studied in immature hypophysectomized rats, taking as criteria the testicular weight and the presence of spermatozoa in the seminiferous tubules. Among these the most active compounds are androstenediol dipropionate, methyl androstenediol, methyl androstanediol, androstenediol, and dehydroisoandrosterone. It is definitely established that the ability of steroids to protect the testis against the atrophy caused by hypophysectomy is entirely independent of the other main pharmacologic activities.

The author is greatly indebted to the following chemists, who kindly supplied the steroids used in this investigation: G. W. Holden of Charles E. Frosst & Co., E. Pike of Gelatin Products Co., C. Scholz of the Ciba Co., and E. Schwenk of the Schering Corp.

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MEIGS' SYNDROME IN A CASE OF MULTILOCULAR PSEUDOMUCINOUS CYSTADENOMA OF THE OVARY*

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The association of fibroma (or fibromyoma) of the ovary with hydroperitoneum and hydrothorax has received increasing attention in the last few years, especially since the classical reports defining this condition were first published by Meigs and Cass[23] in 1937 and by Meigs[19] in 1939. This is demonstrated by the fact that while only scattered

* Believing that, in general, eponymic names of diseases should be restricted closely to the conditions as described by the original author, we asked Dr. Meigs if he thought that the term was justified in this case, which is not a fibroma, as originally described by him. We may say that he thinks that it is justified, and that the various types of primary lesions should be considered, from this point of view in one group. This seems desirable, as the secondary changes—effusions into the serous cavities—are the same following various neoplasms, the leak occurring in an organ without a good capsule.—Editor.

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reports on authentic cases can be culled from the literature between 1879 and 1934, hardly a year has passed since 1937 without reference in some American journal to new cases of ovarian fibromata associated with abdominal ascites and pleural effusion. This clinical entity has appropriately been given the name of "Meigs' syndrome."

The association of benign ovarian tumors other than fibromata with ascites and hydrothorax is also beginning to be reported. Thus Vogt[32] reported a case of granulosa cell tumor of the ovary associated with hemoperitoneum and hemothorax. Traut and Marchetti,[31] analyzing a group of 61 tumors of the "granulosa" type and "theca" cell type for the Society of Gynecological Pathologists of New York, state that, in one of the cases presented, hydrothorax was a prominent symptom and that on operation abdominal fluid was found. The tumor of the ovary proved to be quite benign. McFee[17] reported a case in which a multilocular cystadenoma of the left ovary weighing 17 pounds was found associated with abdominal ascites and hydrothorax. Perlmutter[25] observed this same syndrome where a thecoma of the right ovary was later found at operation. Kelemen[13] has recently reported a case due to a Brenner tumor of the ovary.

In addition, it has been found that benign tumors of the pelvic organs, other than those of ovarian origin, can give rise to the symptom-complex of abdominal ascites associated with pleural effusion. In a personal communication to Meigs,[22] Cullen states that a case of uterine fibroids associated with abdominal and chest fluid[14] referred to in his textbook would, in the light of our present knowledge, fall into this category. Salmon[29] in addition to 1 case of ovarian fibroma with fluid in the peritoneal and pleural cavities, reported a case in which fluid was found in these cavities in association with a large uterine fibroid with interligamentous extension and follicular cysts of the ovaries.

Agreeing with the following statement: "The importance to the internist, as to the gynecologist, of keeping in mind the fact that a benign ovarian tumor may cause hydrothorax as well as ascites and that the simplest of laparotomies uniformly results in complete relief of the thoracic as well as of the abdominal features of the syndrome needs general recognition and emphasis" (Herrick *et al.*[10]), we herewith report a case of pseudomucinous multilocular cystadenoma of the ovary associated with hydroperitoneum and right hydrothorax. In common with all the cases mentioned above, regardless of the origin or of the cellular structure of the benign pelvic tumor, complete cure was obtained in this case. The tumor was removed with subsequent complete recovery of the patient and disappearance of the fluid. This is the true test for a case of Meigs' syndrome.

Report of Case. H. R. (No. 21709), a 39 year old white female, admitted on May 24, 1943, discharged on June 10, 1943, on May 22, 1943, presented herself at the office of one of us (J. M.) with the complaint of shortness of breath on mild exertion. Examination revealed fluid in the right chest from apex to base (confirmed by fluoroscopy), and an enlarged abdomen. Her weight was 135 pounds. Hospitalization was advised, and the patient was admitted to the Mercy Hospital, Rockville Centre, L. I., N. Y., 2 days later.

For 6 to 8 weeks the patient had been complaining of increasing shortness of breath with dry cough in the last 2 weeks. An incidental complaint was the loss of 12 pounds, which the patient states was due to a self-imposed diet, and which she regained recently. The past history revealed that the patient had had bronchitis the winter before. She had 2 children, aged 10 and 17 years. There was no history of miscarriage. The family history was non-contributory.

System review revealed the absence of gastric distress, the appetite to be good, and the bowels regular. On coughing there was no mucus or bloody expectoration, or chest pain. Peripheral edema was absent. Menses were regular with the exception of February, 1943, when she had a period twice in 1 month. There were no urinary disturbances.

The patient sat quietly in bed with a somewhat drawn expression; her face thin, but general nutrition was good. The chest revealed absent breath sounds from apex to base, and dullness to percussion in the right chest. The heart was shifted to the left. The rhythm was regular and there were no murmurs. The blood pressure was 110/70. The abdomen revealed a mass filling the pelvis and extending up to the umbilicus. The cervix was freely movable and the ovaries were not felt.

A diagnosis of malignant neoplasm in the pelvis with metastasis to the right pleural cavity was made. The surgical consultant (J. S.) agreed, and exploratory operation was advised after removal of the chest fluid.

FIG. 1.—Roentgen ray of chest on admission to Mercy Hospital.

Course. The patient had no fever on admission. The urinalysis and blood count were normal. On the day of admission 900 cc. of straw-colored fluid was withdrawn from the chest and sent to the laboratory for examination.

Roentgen ray Report (5/24/43). There is a large amount of free fluid in the pleural space on the right, extending from the level of the diaphragm to the apex. There is a zone of aërated lung at the right of the spine. The mediastinal structures and the lung root are displaced toward the left. There is no evidence of disease of the lungs. There is no destructive bone disease.

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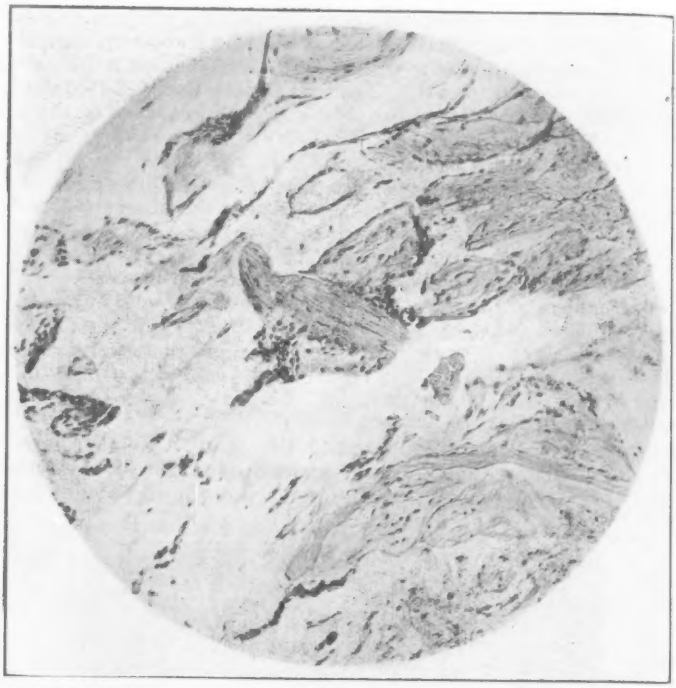

FIG. 2.—Microscopic section of ovarian pseudo-mucinous cystadenoma of ovary.

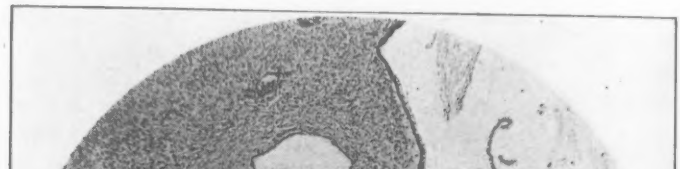

FIG. 3.—Microscopic section of peritoneal implant.

Laboratory Report on Fluid. Smear: no evidence of bacteria. Culture: no growth. Diagnosis: non-maligant transudate.

On May 25, 1943, 900 cc. of chest fluid was removed. The patient broke out into a light warm sweat, and although no discomfort was complained of, the tap was stopped. On May 27, 1943, 1950 cc. of chest fluid was removed without the patient experiencing any discomfort.

Laparotomy (J. S.) (May 28, 1943). A large ovarian cyst was delivered without difficulty. There was a moderate amount of yellow peritoneal fluid, and occasional mucinous implants were noted on the peritoneal surfaces. One peritoneal implant was removed for pathologic examination. The postoperative course was entirely uneventful. The patient ran a temperature of 100° (R) for 2 days. This subsided on the 3rd postoperative day and remained normal for the rest of the stay in the hospital.

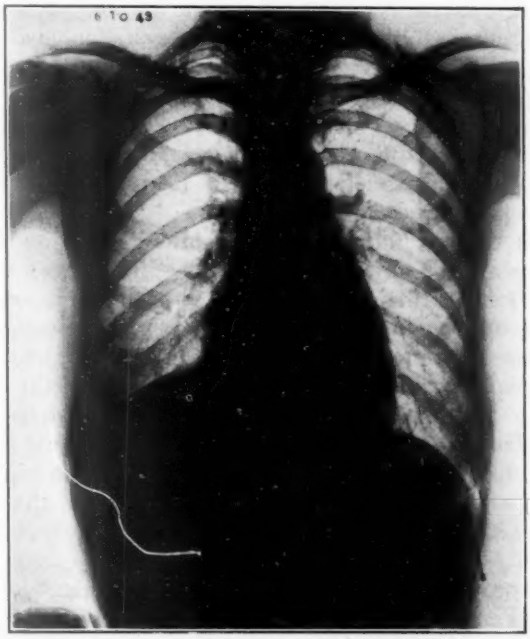

FIG. 4.—Roentgen ray of chest on discharge from Mercy Hospital.

Pathologic Report. On *A*, Cyst; *B*, on peritoneal implant.

A. Specimen consists of a massive ovarian cyst previously sectioned and now showing an interior consisting of numerous locules containing a thick mucilaginous fluid. The attached tube is somewhat elongated and on section shows no noteworthy change. The cyst wall shows numerous small secondary cystic implants.

B. Specimen consists of a small pea-sized mass having a finely villous-appearing outer surface rich in mucinous material.

Diagnosis: *A.* A multilocular pseudomucinous cystadenoma of the ovary. *B.* Peritoneal implantation of tumor tissue. (Dr. Theodore J. Curphey.)

On June 10, 1943, 700 cc. of straw-colored fluid was obtained from the right chest and taken to the laboratory for examination. The guinea pig test for tubercle bacilli, reported several weeks later, was negative.

Roentgen ray Examination (6/10/43). Reëxamination of the chest after 2 weeks and after the removal of 700 cc. of fluid reveals no evidence of free

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fluid in the pleural space. On the right the apex is retracted and there is a small pneumothorax in this area. The interlobular fissure on the right is faintly outlined. The right diaphragm is elevated and tented in its median portion by a pleural adhesion. There is no evidence of metastatic disease in the lung fields.

The patient was discharged on the same day. Her weight was 109 pounds. She was last seen in April, 1944 at which time the pelvic examination was negative and the chest was free of fluid by physical examination and fluoroscopy. Her weight was then 137 pounds, and she felt and looked the picture of health.

Comment. Meigs' syndrome can be regarded by definition as a simultaneous collection of abdominal and chest fluid due to a benign tumor of the pelvic organs.

The etiologic factor is usually a benign fibroma of the ovary; but it can also be a granulosa cell tumor, a cystadenoma, thecoma, or Brenner's tumor. Grossly, these ovarian tumors producing the fluid may vary in size from that of a small orange to that of a 4 to 5 months pregnant uterus. Microscopically, they are usually derived from the various connective tissue elements of the ovary. In none of these cases are any malignant elements found. Rarely benign fibromyomata of the uterus may be a cause.

The production of fluid by these smooth-shelled tumor masses has never been satisfactorily explained. The frequency of abdominal ascites by itself in these cases varies with the series reported, but occurs on the average in about 20% of cases.[6,11,26] In conjunction with chest fluid the percentage must be much less. A recent clinical and pathologic study of 283 cases of ovarian fibromas at the Mayo Clinic by Dockerty and Masson[4a] revealed 3 cases of Meigs' syndrome. Inasmuch as inflammation, pedicle twists, and omental adhesions are infrequently found with these tumors in association with the fluid, and inasmuch as the fluid disappears on removal of the tumors, one must agree with Meigs[22] that there is cause and effect in this connection.

Meigs has proved that the flow of fluid is from the abdominal cavity to the pleural cavity by injecting India ink into the peritoneal cavity of patients with Meigs' syndrome and finding it in the chest fluid in the same concentration later. Following the injection of India ink into the chest cavity, none was found in the abdominal fluid. In addition, he injected air into the chest cavity of one of his patients and tilted her in the Trendelenburg position. After numerous Roentgen rays in various positions, no air was noted in the abdominal cavity. Ritvo reversed this procedure by injecting air into the abdominal cavity by means of a peritoneoscope and noted that no air found its way into the pleural cavity. One may thus rule out pleuro-peritoneal openings in the diaphragm. At present, until further experimental findings prove otherwise, abdominal fluid may be assumed to reach the pleural cavity by way of the lymphatics. Some additional weight to the assumption that abdominal fluid is the source of the chest fluid is that in 2 of Meigs' cases the abdominal fluid and the chest fluid

were identical as to total protein content and as to the electrophoretic distribution of the protein components, namely albumin, alpha, beta, and gamma globulins, and fibrinogen.

Clinically the patient presents a variety of symptoms and a few outstanding physical signs. She is anywhere between 34 and 75 years of age. Her occupation is not significant from a medical viewpoint. The complaints may be of recent origin or they may have been present for years with a recent history of having become worse. The gastrointestinal history is usually that of vague appetite disturbances with perhaps occasional bloating and belching. There is occasional constipation but no diarrhea. The menstrual cycle is apparently not usually disturbed. Rarely is there irregular bleeding either before or after the menopause has set in. She may or may not have had children. One case is reported to have associated with pregnancy and the patient died.[3]

The patient may appear well nourished or she may state that in spite of maintaining her normal weight or even gaining weight, her face looks thin. She may appear acutely, chronically, or gravely ill. Complaints referable to the chest are dyspnea, gradually increasing, either at rest or on moderate exertion. Orthopnea is a prominent symptom. Chest pain is rare, although a "heaviness" in the chest may be felt. Abdominal complaints are usually those of enlargement, with probably bearing down or heavy sensations in the pelvis. Backache and frequency or difficulty in voiding may be experienced. Due to elevation of the diaphragm there may be respiratory embarrassment. Occasionally a history of repeated chest or abdominal taps or both with rapid reaccumulation of the fluid will be obtained.

Important in the diagnosis of Meigs' syndrome is the finding of chest fluid and the finding of an abdominal tumor in association with ascites. Frequently abdominal paracentesis may be necessary before a small or moderately sized tumor can be felt on bimanual examination. Sometimes all that is felt is a large tumor mass, and a moderate amount of fluid will be found in the abdominal cavity on operation entirely out of proportion to the massive amount in the pleural cavity. Frequently all that the patient will complain of is dyspnea. An abdominal tumor will be missed because attention is drawn to the pleural effusion, and pelvic examination will not be done because of lack of complaint localized to this region. A high index of suspicion of Meigs' syndrome should lead to pelvic examination and the demonstration of a tumor.

The differential diagnosis should include the consideration of all the diseases which will produce abdominal fluid and pleural effusion. The diagnosis of malignant pelvic tumors with metastasis to the pleural cavity is the most frequent pitfall in these cases. Particularly where a diagnosis of abdominal tumor has been made sometime before, the sudden appearance of ascites and pleural effusion has been considered *prima facie* evidence of malignancy; yet complete cure of Meigs' syndrome is reported in a case where previously an abdominal

tumor had been known to exist for 8 years.[27] Heart disease, with a rapidly failing heart and accumulation of fluid in serous cavities and tissues, must be ruled out. Peripheral edema and tissue edema is rarely if ever encountered in Meigs' syndrome, however, the coëxistence of these conditions in the elderly female must be borne in mind. Cirrhosis of the liver and tuberculosis must also be considered. In the former, a palpable liver or spleen or both will serve for diagnosis, while in the latter the demonstration of the tubercle bacillus or the finding of a lung lesion on Roentgen ray after paracentesis will clinch the diagnosis.

Laboratory tests on the blood, urine, or ascitic or pleural fluid will not be of any specific aid in the diagnosis of Meigs' syndrome except to exclude other conditions. The ascitic or pleural fluid itself in Meigs' syndrome appears to have no special properties except those expected of a transudate.

The prognosis in Meigs' syndrome is excellent if the ovarian tumor is removed. With the ablation of the tumor, the patient ceases to form abdominal fluid, the pleural cavity clears, and recurrence does not take place. The general health, weight, and entire clinical course improves. Even those patients who seem to appear exhausted and cachectic and have traveled from doctor to doctor or clinic to clinic receiving numerous abdominal and thoracic paracentesis—with rapid reaccumulations of the fluid and continued dire prognosis—do miraculously well after operation. This has happened in spite of the fact that in several of the reported cases the patients were over 70 years of age.

Meigs' syndrome has been elevated to a classical clinical entity, as attested by an increasing literature on the subject. Its importance lies in the fact that it is a benign disease which is easily and permanently cured by laparotomy and removal of the offending tumor. The syndrome is fatal only when misdiagnosed, which places the responsibility of the outcome directly on the shoulders of the medical profession. It is most interesting to note that whenever this subject comes up at a medical meeting,[10,22] at least several of the attending physicians do not fail to recall cases of Meigs' syndrome which they have seen. Some of these cases have resulted fatally, and autopsy has revealed typical cases which could have been saved by early operation. Of the cases that have survived, all the physicians have expressed delight, surprise, and a distinct sensation of relief at the unexpected outcome and smooth recovery of a patient that had been doomed by the preoperative diagnosis of abdominal malignancy with metastasis.

It thus behooves general practitioners, internal medical men, and surgeons to keep this entity in mind when dealing with females who present themselves with chest fluid as a predominant symptom. Pelvic examinations should be done in all these cases and ovarian tumors ruled out by the most careful and scrupulous examination. When the examination of the pleural or ascitic fluid reveals no specific disease surgeons should be encouraged to perform exploratory lapar-

otomy even when in their clinical judgment malignant disease with metastasis seems obvious. This should be done regardless of the apparently exhausted and cachectic condition of the patient.

Summary. 1. Meigs' syndrome may be caused by other benign pelvic tumors than the ovarian fibroma originally described by Meigs.

2. A case of Meigs' syndrome with recovery is reported due to a massive multilocular cystadenoma of the ovary. This is a distinct rarity, as it is the second case to be noted in the literature.

3. Meigs' syndrome is probably not as uncommon as the literature would indicate. The increase in reported cases is most likely due to the increased recognition of the condition rather than to an increase in incidence.

4. Both internists and surgeons should be made more aware of this condition as the outcome of the undiagnosed case is fatal, as compared to the 100% recovery in the properly treated case.

5. More of these cases should be reported as they occur and a registry opened for their tabulation, so that adequate recognition can be given to this syndrome and a true basis of incidence established.

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A RELATION BETWEEN CELL-PACK (HEMATOCRIT) VOLUMES AND LYMPHOCYTE COUNTS*

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In the course of a study of factors affecting the health and efficiency of medical students, a set of numerical measurements or scores were obtained for each of 37 students who volunteered.[6]

One consequence of this was the disclosure of an unexpected relationship, which is the subject of this paper, between cell-pack volumes (hematocrit readings) and the percentage of lymphocytes found in the differential blood count.

The reason for including the cell-pack volume in the study was that a run-down physical condition might reasonably be expected to be associated statistically with anemia, and so with a lowering of the ratio of total corpuscular volume to plasma volume. The reasons for doing the differential counts were: (1) the generally accepted principle that there is likely to be a lymphocytosis in chronic infections and in the aftermath of acute infections,[7] and (2) the impression of physicians that there is a tendency to lymphocytosis in men who are overworking.[4]

Table 1.—Relation of the Number of Lymphocytes to Cell-pack Volume

	Cell-pack volume							
Lymphocytes	39, 40	41, 42	43, 44	45, 46	47, 48	49, 50	51, 52	Totals
15 to 19	..	..	..	..	..	..	1	1
20 to 24	..	..	1	3	..	1	..	5
25 to 29	..	..	2	1	1	3	3	10
30 to 34	..	1	1	4	..	..	..	6
35 to 39	..	1	..	2	2	..	..	5
40 to 44	..	..	1	1	1	1	..	4
45 to 49	1	..	1	..	..	..	..	2
50 to 54	..	1	..	..	..	..	..	1
55 to 59	..	..	..	1	..	..	..	1
	1	3	6	12	4	5	4	35*

Correlation coefficient $r = -0.428 \pm 0.093$.

* Data incomplete for 2 of the 37 subjects.

This paper will also include passing mention of the body weight and the sedimentation rate. The sedimentation rates, cell-packs, and differential counts were all done according to methods that have been in constant use in this laboratory[5] for some years. This latter fact is significant because the phenomenon we wish to report, having first

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caught our attention in the study of the 37 medical students, was then found also to be demonstrable in the records of our dispensary patients.

Table 1 shows that a high lymphocyte percentage was associated with a low cell-pack volume. A consideration of the probable error showed that a correlation coefficient of −0.43 would arise by chance in a sample of 35 subjects about 3 times in 1000.

This result proved to be quite consistent with other conclusions drawn from the study of the 37 students. To illustrate, six of the possible correlations are given in Table 2.

TABLE 2.—COEFFICIENTS OF CORRELATION AMONG BODY WEIGHT, SEDIMENTATION RATE, CELL-PACK VOLUME, AND PERCENTAGE OF LYMPHOCYTES

	Body weight	Sedimentation rate	Cell-pack volume
Percentage of lymphocytes	−0.26	+0.22	−0.43
Cell-pack volume	+0.19	−0.29	
Sedimentation rate	−0.50		

This table indicates, for instance, that a negative correlation (−0.26) was found between lymphocyte percentage and body weight. For 37 pairs of data, coefficients of ±0.30 could arise by chance oftener than 5 times in 100; hence only the coefficients −0.43 and −0.50 in the table are significant by the conventional standard. But it is to be noted that the algebraic signs of the coefficients are in agreement with the assumption that low body weight, low cell-pack, high lymphocyte percentage, and high sedimentation rate are associated with the run-down state and hence with each other. When high is associated with high (or low with low), the sign of the correlation coefficient should be positive; when high is associated with low, the coefficient should be negative. Accordingly, the signs should be these:

	Body weight	Sedimentation rate	Cell-pack volume
Lymphocyte percentage	−	+	−
Cell-pack volume	+	−	
Sedimentation rate	−		

The agreement between theory and results is seen to be perfect.

TABLE 3.—RELATION OF NUMBER OF LYMPHOCYTES TO HEMATOCRIT VALUES

Lymphocytes	Hematocrit 9–11	12–14	15–17	18–20	21–23	24–26	27–29	30–32	33–35	36–38	39–41	42–44	45–47	48–50	Totals
5– 9							1	1	1				1		4
10–14				1			1	1		1		2			6
15–19							2		1	1		1	1	1	7
20–24	1			1	1	2	1	1	5	5	1	2	4	1	25
25–29					1	1	1	4	1	2	4	1	2	3	20
30–34				2	1	2	1	1	2	2	5	5	3	2	26
35–39		1		1	1	2	2	6	4	3	2	3	3	1	29
40–44		1		2	1	1	3	1	2	3	4	1			19
45–49			1		2		3		1	1	3				11
50–54					2	1		1		2					6
55–59								1				1			2
60–64		1								1					2
65–69						1					1				2
70–74															0
75–79															0
80–84							1								1
	1	3	1	7	9	10	16	17	17	21	20	16	14	8	160

Correlation coefficient r = − 0.192 ± 0.052.

Nevertheless, a study was made of the hematologic records of dispensary patients back to and including the year 1936. Records were found for 160 patients each of whom had had cell-pack determinations and differential counts done on the same day. The correlation table obtained by distributing these results showed some interesting features.

The over-all correlation coefficient for this table is seen to be -0.191 ± 0.052, and is significant. It is lower than that given by Table 1; this is evidently connected with the fact that the cell-pack figures for the dispensary patients extend far down below the normal range, where the relation to the lymphocyte percentage is seen to become much vaguer. If one arbitrarily takes as normal the range seen for medical students in Table 1, and takes only the data for the 59 patients whose cell-pack volumes were between 39 and 50, one obtains $r = -0.33$.

Discussion. The negative correlation here found between cell-pack volume and percentage of lymphocytes in the differential count is strongest in the normal range and very much weaker in the subnormal range. This suggests the question whether some reciprocating mechanism may be at work in the normal body, operating in such a way that lymphocyte production would be depressed whenever erythrocyte production is temporarily more active. It is evident that a mere dilution of the blood by increasing its plasma content could not change the proportions among the colorless corpuscles in the differential count.

In favor of the assumption of a reciprocal relation between lymphocyte production and erythrocyte production is the finding by Kracke[1] that there is an increase in the absolute numbers of lymphocytes in the blood of many children with profound hypochromic anemia because of malnutrition.

On the other hand, the phenomenon seen in our own data could be explained on the assumption that from time to time, in the normal body, there is an accelerated discharge of lymph from the lymphatic ducts into the veins. Evidence obtained by Ehrlich and Lazarus[3] and by Rous,[8] indicating that lymphocytosis can be the result of this simple mechanical process, is quoted by Drinker and Yoffey.[2] These authors also point out that this assumption explains only moderate and transient degrees of lymphocytosis, of the sort that would constitute an immediate response of a normal body to some special stimulus like exercise or the administration of a drug. This would be in agreement with our finding that the correlation between lymphocytosis and blood dilution (in the sense of low cell-pack volumes) is best in the normal range.

Summary. Cell-pack determinations in 35 medical students proved to have a significant negative correlation with the percentage of lymphocytes found in the differential count. The same correlation was found in results from 160 dispensary patients; it was strongest in the normal range and was obscured in the subnormal range.

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PERNICIOUS ANEMIA AND CARCINOMA OF THE STOMACH—AUTOPSY STUDIES CONCERNING THEIR INTERRELATIONSHIP*

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The development of any two disease processes in the same individual leads quite naturally to conjectures concerning the nature of their relationship. When both conditions are manifested with considerable regularity, their common etiologic origin may in general be directly inferred. The apparently sporadic concurrence of two diseases in only a few of the many individuals afflicted with one or the other condition presents a much more subtle and difficult problem.

Interest in the coëxistence of pernicious anemia and carcinoma of the stomach dates back as far as 1876, when Quincke is said to have called attention to such a case. Since the turn of the century, increasing numbers of case reports have appeared. This trend appears to have been further accelerated since the advent of specific therapy for pernicious anemia. As a result, several investigations have been conducted to determine whether the two conditions are related etiologically or merely through chance. An even greater amount of attention has been directed to the mechanism upon which this relationship is based.

Further investigation of the problem seems justified inasmuch as certain practical implications of considerable significance may be inferred from such a causal relationship. Accurate analysis of the problem, however, is beset with a great many difficulties, which explains in part the fact that a final answer has not yet appeared.

At least 4 possible relationships become apparent upon *a priori* consideration of the subject:

1. Pernicious anemia and carcinoma of the stomach may appear in the same individual solely through chance, in which case no etiologic interconnection may be inferred.

* Based upon a thesis submitted to the Graduate Faculty of the University of Minnesota by the first-named author in partial fulfillment of the requirements for the degree of Master of Science.

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2. The two conditions may develop concurrently more often than can be explained by the laws of probability, in which case:

(*a*) Carcinoma of the stomach may cause pernicious anemia or a condition so closely simulating it as to defy differentiation.
(*b*) Pernicious anemia may cause the development of gastric malignancy.
(*c*) A factor common to both conditions may act as a precursor of each and serve to explain their coëxistence.

Statistical treatment of the problem requires the accumulation of adequate and accurate data. It is at this point that some of the major difficulties involved become apparent. For many years, conclusive criteria for the diagnosis of pernicious anemia were lacking. The earlier investigators were therefore confronted with the dilemma of proving that true pernicious anemia was present in the cases studied. This diagnostic difficulty has been diminished to some extent by the elucidation of newer and more stringent criteria, but the diagnosis of pernicious anemia still requires a considerable amount of clinical and laboratory data of rather specialized nature. Many of the previous publications on this subject have suffered from a lack of data adequate to permit a clear-cut diagnosis in all cases.

Emphasis has long been laid upon the well-known fact that a macrocytic type of anemia which superficially resembles pernicious anemia may occur in patients with gastric cancer. As a result of this emphasis, there appears to be a widely held view that any macrocytic anemia encountered in association with a gastric malignancy is secondary to the neoplasm. Both clinicians and pathologists have therefore been prone to discard an initial diagnosis of pernicious anemia in favor of a secondary anemia in such cases. This appears to have occurred even in numerous instances in which the evidence of pernicious anemia has been entirely convincing. To date, no analysis of autopsy data pertinent to the problem has taken such diagnostic errors into consideration. The present study was undertaken in an attempt to elucidate further evidence concerning the relationship of pernicious anemia to carcinoma of the stomach by a review of autopsy material.

Review of the Literature. Extensive reviews of the published case reports and of other evidence bearing upon the problem have been presented by Cotti,[8] Washburn and Rozendaal,[41] and Jenner.[20] To avoid reduplication of effort, no exhaustive review has been attempted here. Among the many case reports of coëxisting pernicious anemia and gastric carcinoma which have appeared in recent years are those of Nesler,[29] Bronstein,[4] and Hagyard.[15]

A series of publications based upon large numbers of cases of pernicious anemia has issued from the Mayo Clinic in the past 20 years. The results noted illustrate strikingly the apparent trend to an increasing coëxistence of the two diseases. In 1923, Giffin and Bowler[13] noted only 1 gastric carcinoma and 4 other malignant neoplasms in a series of 628 patients with pernicious anemia. Conner and Birkeland[7] encountered 20 cases of coëxistence of pernicious anemia and carcinoma of the stomach among 658 patients with the former disease seen in the period from 1925 to 1930. The next report was that of Washburn and

Rozendaal,[41] who found 11 more such cases in the ensuing 3-year period. Recently, Doehring and Eusterman[9] reported on 1014 cases studied from 1935 to 1939, of which 17 also had carcinoma of the stomach. They stated that a total of 40 such cases has been noted at the Mayo Clinic since 1917, in 26 of which the diagnosis of pernicious anemia was established before symptoms referable to the gastric neoplasm became apparent.

Multiple cases of coëxisting pernicious anemia and gastric carcinoma have been reported by Jenner,[20] Fitz-Hugh,[12] Strandell,[36] Cotti,[8] Hurst,[18] Murphy and Howard,[28] Rigler,[31] and others. In many of these cases blood disease existed for many years before the malignant neoplasm supervened. Thus, a patient reported by Miller[26] gave evidence of pernicious anemia for 17 years prior to the development of a gastric carcinoma. Pernicious anemia was present for 4 and 6 years, respectively, in the 2 cases reported by Cotti,[8] before symptoms of the gastric tumor were noted. Doehring and Eusterman[9] found in their series that the average interval between the onset of symptoms of pernicious anemia and those of carcinoma of the stomach, in cases where such a determination could be made, was 8.7 years.

The association of pernicious anemia with gastric neoplasms is not limited to carcinoma. Adenomatous polyps have also been encountered frequently in patients with Addisonian anemia. Washburn and Rozendaal[41] noted 8 such cases, and Doehring and Eusterman[9] later added 4 more. Six cases were observed by Velde[40] in a series of 42 patients with pernicious anemia, an incidence of 14%. In a control series of 1271 patients with a variety of other diseases, the incidence of gastric polyps was only 0.71%. Haring[16] reported 7 cases of coëxistent gastric polyps and pernicious anemia. Three such cases were encountered by Schindler and Serby[34] in a gastroscopic study of 23 patients with pernicious anemia. Numerous other cases have been described; however, no attempt has been made to compile all such instances.

The coëxistence of gastric polyps and pernicious anemia is particularly important in view of the apparently precancerous nature of such polyps. Miller, Eliason, and Wright[27] in 1930 collected 24 cases in which adenomatous polyps had progressed to frank gastric carcinoma and added 8 cases personally observed in a series of 23 gastric resections for polyps. The incidence of malignant degeneration in their cases was 35%. Stewart[35] found carcinoma associated with 13 of 47 gastric polyps. Nine of the 50 polyps noted by Lawrence[23] showed histologic evidence of malignancy. McRoberts[25] carefully studied 5 cases of gastric polyps and found histologic evidence of "carcinoma *in situ*" in 4 of them. Similar evidence of malignant change was found by Haring[16] in 4 of his 7 cases. Rigler and Ericksen[32] found malignant degeneration in 4 of 25 polyps detected roentgenologically, and in 4 of 31 encountered in studies of autopsy material. In 7 instances noted by Benedict and Allen[1] among a series of 17 polyps, malignant features became manifest upon histologic study of the resected tumor, or the patients later died of gastric carcinoma. Thus, it would appear

that the demonstration of gastric polyps in association with pernicious anemia has almost the same significance as the demonstration of carcinoma *per se*.

In addition to the case reports enumerated above, there have been a few systematic and thorough investigations based upon both autopsy and clinical material. Rambach[30] found 641 cases of gastric carcinoma and 50 cases of pernicious anemia in a series of 11,849 postmortem examinations. On the basis of chance alone, the incidence of coëxistence of the two diseases is the product of their respective incidences, or approximately 2.4 cases for the entire series. Actually, 11 cases of combined pernicious anemia and gastric carcinoma were encountered which represents a statistically significant deviation. In a small series of 22 cases of pernicious anemia studied by Brandes,[3] 4 carcinomas of the stomach were observed at autopsy, an incidence of 18%. Jenner[20] reviewed the autopsy findings in 76 patients with pernicious anemia, and noted 5 gastric carcinomas and 4 benign gastric tumors. Only 1 other malignant tumor was observed, which arose in the uterus. Among a total of 18,200 postmortem examinations recorded between 1897 and 1933, Madeleine Brown[5] found a total of 151 cases of pernicious anemia, of which 12 (8%) had gastric polyps, and 1 additional case had a gastric carcinoma. The incidence of gastric polyps among the remaining autopsies was only 0.003% in her study. The control figure given must be in error, however, and the more generally accepted autopsy incidence of 0.5% may be used for comparison.

One of the most extensive clinical studies which has appeared is that of Jenner.[20] He found 8 cases of associated gastric carcinoma in a series of 181 patients with well-authenticated pernicious anemia. By applying the corrected mortality incidence of carcinoma of the stomach to the living population of the city of Amsterdam he arrived at the morbidity incidence for gastric cancer in various decades. Comparison of this incidence with that in his pernicious anemia patients revealed that the incidence of gastric neoplasms in the latter group was at least 12 times as high as that in the general population of corresponding age. Similarly, Van der Sande[39] developed morbidity statistics for gastric carcinoma, and calculated the expected incidence of coëxistence of the 2 disease processes. This was then compared with the actual incidence of association as reported in various earlier publications, and again the actual frequency was obviously far higher than that expected on a chance basis.

Cotti[8] presented a compilation of published cases of pernicious anemia associated with some form of malignant tumor. He found that among 107 cases of this type, the neoplasm was primary in the stomach in 93, or 86%. It is generally considered that gastric carcinoma represents about 30% of all malignant tumors coming to autopsy, and its relative incidence in living individuals is somewhat less than this value. The proportion of gastric malignancies encountered by Cotti is therefore far beyond that which would be expected upon a probability basis.

It is apparent, therefore, that evidence is available which is at

least strongly suggestive of an etiologic relationship between pernicious anemia and gastric carcinoma. We are not primarily concerned here with the mechanism of this relationship. Only a brief outline of the mass of evidence pertinent to this phase of the subject will therefore be considered.

A number of investigators have pointed out the tendency of patients with gastric carcinoma to develop anemia of macrocytic type, and have also considered this neoplasm a possible cause of true pernicious anemia. In the light of the classical work of Castle and his collaborators, this view was supported by the argument that destruction of the gastric mucosa by the tumor might lead to a loss of the "intrinsic factor," and could thus eventuate in pernicious anemia. However, attempts by a great number of other investigators to produce anemia in animals by the operative removal of the stomach and in some cases of portions of the small intestine as well have all led to failure. Similarly, very few patients among the great number annually subjected to gastrectomy ever develop true pernicious anemia. Thus, Doehring and Eusterman[9] report that follow-up examinations of 575 gastrectomized individuals yielded not a single case of pernicious anemia. Furthermore, the occurrence of pernicious anemia in patients with very small tumors which could scarcely destroy much of the gastric mucosa tends to refute this contention. It appears doubtful, therefore, that carcinoma of the stomach is a direct precursor of pernicious anemia.

The next possibility to be considered is that, conversely, pernicious anemia may be a precursor of gastric carcinoma. It is at once obvious that pernicious anemia *per se* can hardly be considered the main or the only cause of malignant gastric neoplasms, inasmuch as the latter occur far more frequently. However, there is almost no evidence to establish or refute the possibility that pernicious anemia may be only one, perhaps a very minor one, among several causes of carcinoma of the stomach. The literature of experimental cancer research is replete with examples of multiple causes of several varieties of cancer. It is therefore quite possible that the causes of gastric cancer are likewise multiple.

The final consideration is that a factor common to both conditions may be a precursor of both, or a concomitant of one and precursor of the other. Among the factors of this type which have been enumerated are gastritis, achlorhydria and achylia, constitutional and hereditary factors, and liver therapy for pernicious anemia.

Konjetzny[22] and others have been enthusiastic proponents of the thesis that chronic gastritis, particularly of the atrophic type, is a precancerous lesion. This view is based upon the frequent demonstration of gastritis and of proliferative mucosal changes in the vicinity of malignant gastric neoplasms. However, the recent careful studies of Guiss and Stewart[14] and of Hebbel[17] indicate that chronic gastritis occurs very commonly in individuals past middle age, and is no more frequently associated with gastric cancer than with malignancies primary elsewhere or with non-neoplastic diseases.

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The corollary thesis, that gastritis is a cause of, or is associated with, pernicious anemia, was enunciated by Faber[11] and Hurst.[19] However, Magnus and Ungley[24] studied fresh gastric specimens of individuals dying of pernicious anemia and found no evidence whatsoever of inflammatory change. The only constant finding was atrophy of the mucosa in the fundus and corpus of the stomach. Moreover, it has been demonstrated gastroscopically that the apparent gastritis and atrophy noted in pernicious anemia patients may and often does disappear following adequate liver therapy.[21] Despite the disappearance of atrophic gastric changes in such patients, they may go on after a number of years to the development of gastric carcinoma, as in the cases of Dyke and Harvey.[10]

Haring[16] and others have suggested that achlorhydria and achylia gastrica represent a functional deficiency of the gastric mucosa, which may lead, in an attempt to compensate for the deficiency, to hyperplasia, proliferation, and finally to the development of neoplasms. This theory is somewhat analogous to the known proliferative overgrowth of the thyroid gland in the presence of iodine deficiency. However, the frequency of achlorhydria is so great in relation to the incidence of gastric carcinoma that it must be doubted whether it constitutes a direct cause of the malignant condition. Pending the appearance of further evidence pertinent to this question, the rôle of achlorhydria and achylia in gastric carcinogenesis remains in dispute.

Conner[6] effectively demonstrated the hereditary basis of achlorhydria in pernicious anemia patients. A number of other authorities have reported the occurrence of pernicious anemia in several members of the same family in one or more generations. The evidence for a hereditary and constitutional factor in the development of gastric carcinoma is likewise suggestive. Finally, the occurrence of one or both of these diseases in several members of a single family has been reported by others.[2,38] There is, therefore, some evidence, admittedly far from conclusive, to indicate that hereditary factors conditioning the development of both pernicious anemia and gastric carcinoma may be linked in some manner to explain the coëxistent occurrence of the two diseases in the same individual.

The final hypothesis requiring mention is that of Teufl,[37] who suggested that the increased incidence of gastric carcinoma in pernicious anemia patients since the advent of liver therapy was due, not to the greater longevity of these patients, but to a carcinogenic effect of the therapeutic liver preparations. Despite our knowledge of the experimental production of skin and subcutaneous tumors in mice by local application of certain liver extracts, this hypothesis remains largely unsubstantiated.

The Present Investigation. *Material and Procedure.* This investigation is based upon a study of pertinent cases among a total of 43,021 consecutive autopsies recorded in the Department of Pathology of the University of Minnesota during the period from 1915 to 1943. Although all cases of pernicious anemia were supposedly recorded in the departmental index, it was felt that an unknown number of additional cases might have occurred in associa-

tion with gastric carcinoma and with other diseases in which the diagnosis of pernicious anemia was discarded or unrecognized at the time of the postmortem examination.

Therefore the problem was approached in several ways in an attempt to obtain a reasonably correct incidence of the association of carcinoma of the stomach with pernicious anemia. The first series of cases included all autopsies in which pernicious anemia was listed among the postmortem diagnoses. After elimination of certain cases in which some evidence was available to refute the diagnosis of pernicious anemia, Series 1 was found to have a net total of 146 cases. These were then carefully studied for the incidence of benign and malignant gastric and other neoplasms.

Series 2 is comprised of all cases of gastric carcinoma occurring in the period studied. Of 1010 such cases, 694 were found to have clinical and laboratory data recorded in the autopsy protocols which were regarded as adequate to either exclude or clearly establish the diagnosis of pernicious anemia. A critical review of these data yielded a considerable number of additional cases of coëxisting pernicious anemia which had not been encountered in the study of Series 1. With this preliminary evidence to support the hypothesis outlined above, concerning the inaccuracy of autopsy diagnoses of pernicious anemia, the next procedure was a parallel review of a large number of cases of another form of gastro-intestinal malignancy. Series 3 consisted of all cases of carcinoma of the colon, rectum, and cecum; of 775 cases, 509 had adequate clinical and laboratory data.

The finding of "occult" cases of pernicious anemia during a study of Series 2 and 3 suggested that perhaps additional cases were similarly unrecognized in association with other malignant conditions or with non-neoplastic diseases. The task of reviewing all autopsies in the entire series for the corrected total incidence of pernicious anemia would have been overwhelming. It was therefore decided to review critically all autopsies in individuals of a selected age group in certain sample years. The percentage of "occult" cases of pernicious anemia detected in these years could then be applied to the total number of individuals of the designated age group in the entire autopsy population to arrive at the total number of cases believed to have been unrecognized. Addition of this group to those already accepted as pernicious anemia would yield the corrected total incidence of pernicious anemia among individuals of roughly comparable age. This figure is necessary to compute the incidence of association of gastric carcinoma and as a basis for statistical analysis.

From this outline of procedure it becomes evident that the value of the entire investigation hinges upon the accuracy with which the diagnosis of pernicious anemia can be established by such a retrospective analysis of data available in autopsy protocols. The only procedure possible at autopsy which would be of any diagnostic value is a study of the bone marrow. Unfortunately this is impossible in most autopsies due to rapid postmortem autolytic changes. In addition, many cases of pernicious anemia die in remission, from some intercurrent complication, at a time when the bone marrow does not present a characteristic picture. The diagnosis, therefore, usually rests wholly upon data obtained during life; diagnostic procedures yielding questionable values cannot be repeated and there are often gaps in the information required for a clearcut diagnosis which can no longer be filled in.

In general, it may be stated that the diagnosis of pernicious anemia was excluded in all cases in which one or more clinical features incompatible with or rarely encountered in this disease were encountered. The diagnosis was accepted only in those cases presenting clear-cut data of characteristic nature; in rare instances cases with incomplete but otherwise acceptable data were included. All other cases with incomplete data were not considered as having pernicious anemia. The diagnostic criteria were adhered to with particular rigor in Series 2, composed of cases of gastric carcinoma.

Results of the Investigation. A total of 27 tumors was encountered among 146 cases of pernicious anemia constituting Series 1. Of these,

only 11 originated extra-gastrically. There were 9 cases of carcinoma and 7 with polyps of the stomach. In 1 case, multiple polyps were present. Six extra-gastric malignancies were noted, arising in the prostate in 3 cases, and in the kidney, breast, and urinary bladder in 1 case each. The 5 benign extra-gastric tumors originated in the uterus, sigmoid, appendix, and small intestine. In this incomplete study alone, gastric tumors of either benign or malignant nature constituted 60% of all observed neoplasms.

In addition to the 9 cases of coëxistent pernicious anemia and gastric carcinoma noted above, 27 cases of the former disease which had been discarded or not clearly recognized at autopsy were encountered in Series 2 among 694 cases of carcinoma of the stomach. Thus a total of 36 individuals had both diseases in this autopsy series. As stated in a preceding section, an additional number of cases may well have had pernicious anemia, but were not included as such because of incomplete data.

Similarly, the parallel study of Series 3, consisting of 509 cases of carcinoma of the colon, rectum, and cecum yielded 4 cases of previously unrecorded pernicious anemia. This also represents the total incidence of coëxistence of the 2 diseases, inasmuch as no cases were encountered in Series 1. Comparison with the incidence of pernicious anemia in cases of gastric carcinoma at once reveals the much higher frequency with which pernicious anemia is associated with gastric malignancies than with malignant tumors arising elsewhere in the gastro-intestinal tract. The incidence was 5.1% among 703 cases of gastric carcinoma and only 0.8% in 509 cases of carcinoma of the colon, rectum, and cecum.

All autopsy protocols of individuals 45 years of age or over were reviewed in the sample years 1920, 1930, and 1940 to obtain the percentage of unrecognized or discarded cases of pernicious anemia in these years. In many instances, the autopsies concerned individuals who were found dead or who died suddenly as a result of trauma or other cause. Clinical data in such cases were either completely lacking or grossly inadequate to exclude the possibility that pernicious anemia might have been present during life. These cases were therefore omitted from study.

In the year 1920, there were only 38 cases with adequate data for study among 180 individuals of proper age. No instances of unrecognized or discarded pernicious anemia were encountered in this small group. In 1930, there were 942 autopsies on individuals of the selected age group, of which 384 had adequate clinical data to establish or refute the diagnosis of pernicious anemia. Only 2 cases of "occult" pernicious anemia were discovered in this year, both in individuals dying of non-neoplastic diseases. The year 1940 yielded 5 more cases of "occult" pernicious anemia among 917 autopsies acceptable for analysis. Four of these 5 occurred in association with non-neoplastic disease. Thus a total of 7 cases of pernicious anemia was unearthed from a study of 1339 individual autopsy protocols, an incidence of 0.5%.

Of the individuals in these 3 sample years 54% were 45 years of age or over. Applying this percentage to the entire autopsy period, we find that a total of 23,231 autopsies were performed upon individuals of the designated age range. The number of "occult" cases of pernicious anemia for the entire period is therefore 0.5% of this total, or 116 cases. An additional 31 cases were noted in the study of Series 2 and 3, bringing the total of unrecognized cases to 147. To these must be added the 146 known cases from Series 1; the estimated total in the entire autopsy series, arrived at in this manner, is 293 cases of pernicious anemia, limited almost entirely to individuals 45 years of age or over.

There were 36 cases of known association of pernicious anemia and carcinoma of the stomach among the 293 cases of pernicious anemia believed to have occurred. This represents an incidence of gastric carcinoma, among all cases of pernicious anemia coming to autopsy, of 12.3%. The incidence of gastric carcinoma among all other autopsied individuals of comparable age was slightly less than 4%, less than one-third of that found in individuals with pernicious anemia.

Statistically, the incidence of expected coëxistence is the product of the respective incidences of the two diseases. Thus, on the basis of chance alone, 5 individuals per 10,000, or a total of 12 cases among the 23,231 cases of the selected age range, would be expected to exhibit both conditions. The actually observed number of cases was 36, and the difference between the observed and expected incidence was therefore 24 cases. The standard error was found to be 3.41 and the ratio of the observed difference to the standard error is 7.40. The probability that the observed result is due merely to chance was found to be less than 1 billion.* This constitutes conclusive statistical evidence of an etiologic relationship between carcinoma of the stomach and pernicious anemia.

Discussion. The establishment of an etiologic relationship between pernicious anemia and carcinoma of the stomach has many important implications. It directs attention to the factors underlying the occurrence of carcinoma of the stomach as outlined above. Further investigation of the hereditary or constitutional factors involved is clearly indicated. Secondly, the knowledge that individuals with pernicious anemia are prone to develop carcinoma of the stomach indicates the necessity for frequent examination of such patients in order to make the diagnosis at as early a stage as possible. A study of the utility of the routine Roentgen examination, at semi-annual intervals, of all individuals with pernicious anemia has been reported elsewhere.[33] Finally, the frequent occurrence of carcinoma of the stomach in a select, readily chosen group of individuals, should permit an adequate study of the early signs and symptoms and of the development and course of carcinoma of the stomach from its incipiency.

Summary and Conclusions. 1. Data in the literature indicate the probability that pernicious anemia and carcinoma of the stomach occur frequently in the same individual.

* We are greatly indebted to Prof. A. E. Treloar of the Division of Biostatistics for aid with the statistical analysis of the results of this investigation.

2. The theories as to the reasons for the coincidence of the 2 diseases are reviewed.

3. A study of 23,231 autopsies on individuals 45 years of age or over is presented.

4. In 293 cases of pernicious anemia, found in this series, 36 also had carcinoma of the stomach, an incidence of 12.3%, which is over three times as great as the incidence in the remaining autopsy population of the same age.

5. Unequivocally the statistics indicate that there is an etiologic relationship between pernicious anemia and carcinoma of the stomach.

6. Patients with pernicious anemia should therefore be examined frequently to detect the onset of carcinoma of the stomach.

We are indebted to Drs. C. J. Watson and Macnider Wetherby for many valuable suggestions and to Dr. E. T. Bell for the privilege of studying the autopsy material from his department.

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CORONARY INSUFFICIENCY, REVEALED BY ECTOPIC NODAL AND VENTRICULAR BEATS IN THE PRESENCE OF LEFT BUNDLE BRANCH BLOCK

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Because the ECG signs of recent myocardial infarct are often obscured by intraventricular block, Dressler's recently published report[1] that myocardial infarct was indicated by 2 ventricular premature beats, although the regular beats, in the presence of left bundle branch block, failed to display significant changes, is important. In this report a similar case is presented in which the electrocardiographic material is even more complete, because more premature beats and more tracings are available. The regular beats fail to give definite evidence of myocardial infarction in the presence of left bundle branch block.

Case Report. The patient, a white male, was 75 years of age. The past medical history was essentially negative except for an episode, 10 years ago, of pain "between shoulder blades in the middle of back" similar to that of the present illness. Pain was of gradual onset, lasted for a few days, and was relieved by heat and rest. He returned to his usual work without any symptoms related to his cardiovascular system. About 2 weeks before hospitalization (3/20/44), following moderate exertion, patient experienced an intense pain localized over the fourth dorsal vertebra posteriorly. At first it was relieved by heat. Within 10 hours the pain became agonizing and radiated down the left arm to the little finger and around his neck and both clavicles. Nausea was slight, weakness and sweating were moderate. Dyspnea was not present. These symptoms were only partially controlled by heavy narcotic sedation, varied in intensity for about 12 days climaxing in a status anginosus on admission to the hospital. Physical examination on admission to the hospital revealed a well-nourished male with only a moderate degree of arteriosclerosis as evidenced by his fundi and slight beading of his peripheral vessels. There were no physical signs of shock; color good; very little dyspnea. Heart sounds were distant, no murmurs, no friction rubs detected. Blood pressure right arm 190/118, left arm 148/90. Lungs were clear. Abdomen negative. Pulse 98 per minute, irregular. Clinical course: During the first 72 hours patient was treated with the usual narcotic and barbiturate sedation, intravenous papaverine and oxygen. His pain gradually subsided. Temperature varied from 99.4° to 100.4° F. However, his pulse became very irregular. Quinidine was started 72 hours after admission. Twelve hours later patient had an episode of syncope, sweating, pulse 48 per minute, blood pressure 100/60. Apex tones were very distant. Over a period of 6 hours the blood pressure returned to right arm 136/70, left arm 116/62. The blood pressure remained at these levels throughout the remainder of his illness. Quinidine therapy was continued at 20 gr. daily. After 40 days the patient was discharged from the hospital ambulatory and symptom-free. Temperature

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remained normal after the 8th day of admission to hospital. Kline was negative. Except for a trace of albumin on admission, urine was negative. R.B.C. 4,460,000, hemoglobin 15.5 gm., W.B.C. 20,700 on admission to 16,750 on 4th day, non-segmented polys varied from 17 to 26% the first 4 days. Sedimentation rates: 3/23/44, 52% after 60 minutes (3rd day of admission); 3/30/44, 59% after 60 minutes (10th day of admission); 4/25/44, 90% after 60 minutes (35th day of admission).

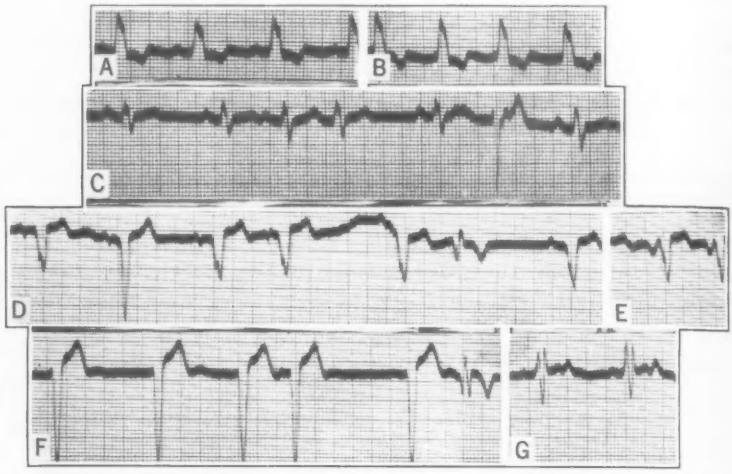


FIG. 1.—*A* and *B*, Lead 1; *C*, Lead 2; *D* and *E*, Lead 3; *F*, Lead CF_2; *G*, Lead CF_4. *D* and *F* show a premature ventricular beat with coronary insufficiency configuration (obscured in the regular beats by left bundle branch block).

Description of Electrocardiograms. The first tracing was taken 24 hours after admission to the hospital, *i. e.*, about 2 weeks after the beginning of the attack. The ECG shows left bundle branch block (QRS interval 0.14 second) and a peculiar type of arrhythmia in Lead 1. Runs of sinus rhythm of lower frequency (Fig. 1*a*, Lead 1 [4 beats]) change with a faster nodal rhythm (Fig. 1*b*, Lead 1). In Lead 2 (Fig. 1*c*) QRS is about equiphasic, the third and fourth beat premature auricular (P coinciding with T), the sixth probably premature ventricular with a much taller and peaked T wave. No preceding P wave is visible, and the fact that the pause is not fully compensatory might be due to the existing sinus arrhythmia. In Lead 3 (Fig. 1*d*) the QRS interval in the regular beats is 0.12 second; the P wave is diphasic in the first 3 beats, but the second QRS complex is much larger and narrower (QRS = 0.1 second). The sixth beat is probably premature ventricular with a prominent notched Q wave of 4 mm. and an inverted T wave of −3.5 mm. The QRS interval is 0.12 second. It is noteworthy that this beat occurs after an excessively long R–R interval of 1.23 second. This beat is followed by a positive P wave. At the end of this lead there is a run of 12 faster, regular, nodal beats with inverted P wave, 2 of them shown in Figure 1*e*, obviously from a different focus than in Lead 1, because of the longer P–R interval. In Lead CF_2, the first 3 beats of Figure 1*f* show irregular sinus rhythm,

the fourth beat is premature, probably nodal, followed by a compensatory pause; the last beat of Figure 1*f* is a premature ventricular beat (QRS W-shaped) with a large Q wave (4.5 mm.) and an inverted T of 4.5 mm. This premature beat is preceded by an R–R interval of 1.24 second. The same episode was repeated at the end of Lead CF_2. No premature ventricular beats occurred in Lead CF_4 (Fig. 1*g*). Another ECG was taken after 24 hours. Figure 2*a* shows Lead 1. The second, third, sixth and seventh beats are the regular beats, initiated by a P wave with a P–R interval of 0.16 second and a QRS interval of 0.12 second. Blocked P waves are seen after the third, sixth and seventh beats. The first, fourth, fifth and ninth beats are preceded by

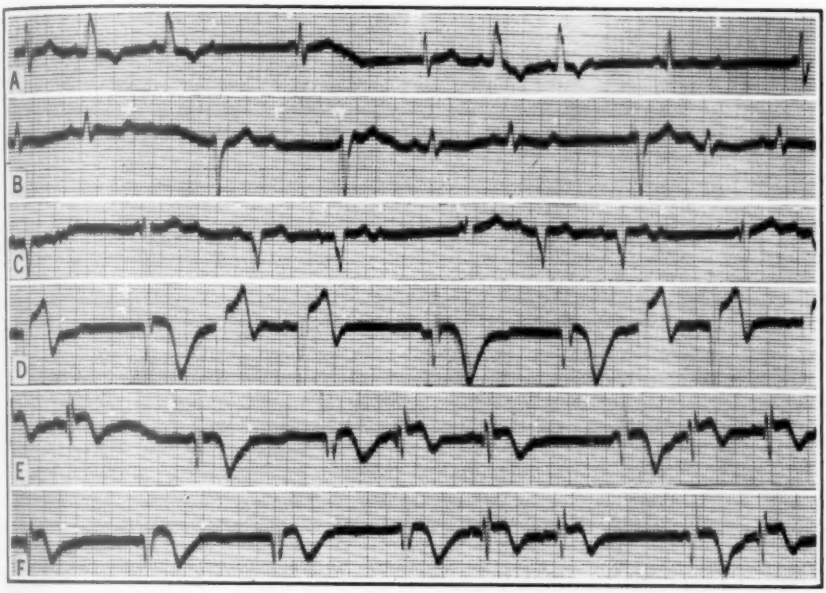
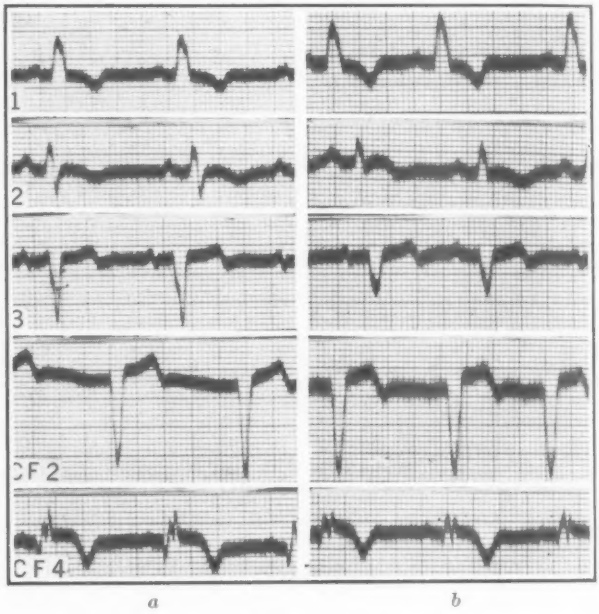


FIG. 2.—*A*, Lead 1; *B*, Lead 2; *C*, Lead 3; *D*, Lead CF_2; *E* and *F*, Lead CF_4. Ectopic beats in all leads (nodal or ventricular escape), most with shorter QRS interval than the regular beats with left bundle branch block. In Leads CF_2 and CF_4, the ectopic beats (2 different types in Lead CF_4) reveal the pattern of coronary insufficiency (increase of Q and inverted T compared with Figure 1). For further details see text.

a P wave with short P–R interval (0.06 second), therefore of nodal origin, with aberrant ventricular conduction resulting in an equiphasic QRS complex with a QRS interval of 0.1 second. The eighth beat is preceded by a P–R interval of 0.13 second; the QRS is up and of normal contour (QRS = 0.08 second). All following 16 beats of Lead 1 resemble the regular beats of Figure 2*a;* they are not included in Figure 2. The first 2 and the last 3 beats of Figure 2*b* show the regular sinus beats of Lead 2; blocked P waves occur after the second, third and sixth beats; the third, fourth and seventh beats are ectopic, the seventh beat obviously nodal, the others probably nodal because of the similar contour with beat 7. All 3 ectopic beats occur after a blocked P wave and are probably due to nodal escape. The same mechanism can be ob-

served also in Lead 3 (Fig. 2*c*) after the first, fourth and seventh beat. The regular beats of Lead CF_2 show a downward QRS deflection. Six ectopic beats were observed in this lead, all with a large Q wave of 8 mm. and a tremendous inverted T wave. Figure 2*d* shows 3 of these beats. None is followed by a compensatory pause, but the interval to the preceding QRS is excessively long (1.40, 1.40, 1.42, 1.42, 1.43, 1.40 seconds). They are due to escape mechanism, possibly ventricular. A notching at the end of the preceding T wave (marked by a dot) is probably a blocked P wave. The QRS interval of the regular beats is 0.12 to 0.13 second, that of the ectopic beats is 0.10, 0.08, 0.11, 0.10, 0.11 and 0.13 second; except the last one, there is a tendency to shorter QRS intervals. In Lead CF_4 (Fig. 2*e*) the regular beats show poly-



a *b*

FIG. 3.—*a*, ECG after 10 days; *b*, after 1 month.

phasic QRS, with a small Q wave, S–T elevation and diphasic T wave. Eight ectopic beats were observed in this lead of 2 different types: (1) diphasic of Q–R type, with a large Q wave of about 6 mm. and an inverted peaked T wave of large amplitude (9 mm.); (2) triphasic W-shaped QRS with a Q and an R wave of about 4 mm., and an inverted T wave of 6 to 7 mm. amplitude. Figure 2*e* shows 3 ectopic beats, the first and third ectopic beat of Type 1, the second ectopic beat of Type 2; the other beats are the regular sinus beats. Figure 2*f* shows, after a regular beat, 3 consecutive beats of Type 2 and, the second last, of Type 1. The QRS interval of the regular beats is 0.12 to 0.13 second, that of the ectopic beats Type 1 is 0.09 to 0.10 second, of Type 2, 0.12 second. The Type 1 ectopic beats are preceded by a P wave with

short P–R interval, while only 1 of 3 ectopic beats of Type 2 is preceded by a diphasic P wave with short P–R interval (second beat, Fig. 2*f*). The R–R interval between the ectopic beats and the preceding beat is excessively long (about 1.40 second). The mechanism for the ectopic beats Type 1 is nodal escape, and for Type 2 nodal or ventricular escape. Blocked P waves are marked with a dot. Further tracings were taken after 3 days, 10 days, 15 days, 1 month and 2 months. Figure 3 shows the tracings taken after 10 days and 1 month later (3*a* and 3*b*). No further ectopic beats could be observed. The evolution of infarct is largely obscured by the left bundle branch block. Noteworthy is the Q wave in Lead CF_4, associated with a sharply inverted T wave.

Discussion. We are not in a position to prove by autopsy that an infarction has occurred, since the patient recovered. The ectopic beats with Q waves and T inversion in Leads 3 and CF_2 of the first electrocardiogram (Fig. 1) and in the chest leads of the second one (Fig. 2) reveal a type of acute coronary insufficiency. The increasing T inversion in the ectopic beats of the second ECG, 24 hours after the first one, is obviously faster than it usually occurs in the evolution of myocardial infarct. The further development is obscured by the left bundle branch block, no further ectopic beats could be observed in the later electrocardiograms. However, the prominent Q wave in Lead CF_4, associated with a sharply inverted T wave (Fig. 3) a few weeks after the attack, is suspicious of infarct, since Q waves in the chest leads of uncomplicated left bundle branch block are rare.[5] The clinical picture was compatible with that of coronary occlusion. Therefore, we think that a myocardial infarction of the septum probably occurred. In any case, the ectopic beats indicate an acute coronary episode, which is not revealed in the regular beats. Dressler[1] offers two explanations for a similar phenomenon in his case: (*a*) occasionally, premature ventricular beats may originate from a focus so located that the excitation wave activates the two ventricles which, in the presence of intraventricular block, are activated one after another in approximately normal sequence;[4] (*b*) when, in left bundle branch block, premature beats originate in the left ventricle late in diastole at the time when the normal sinus excitation is due in the ventricles, the opposed effects of the dextrocardiogram (due to the normal excitation) and of the levocardiogram (due to the premature excitation) may produce an approximately normal ventricular complex.[6] The latter possibility could be ruled out in Dressler's case. One would expect in both mechanisms (*a* or *b*) a shorter QRS interval in the premature beats, while in Dressler's case the QRS interval is about the same in the regular and in the premature beats. The ectopic beats of the second electrocardiogram (Fig. 2), especially in Lead 1 (Fig. 2*a*) and Lead 3 (Fig. 2*c*), have a much smaller QRS interval than the regular beats; in fact, in most of these beats the QRS interval is within normal limits with a normal QRS contour; this is especially true for the eighth beat in Figure 2*a*. Many of the ectopic beats are preceded by a short P–R interval, so that they are of nodal origin. This excludes both mechanisms *a* and *b*. Theo-

retically, a mechanism similar to *b* could be assumed, in that a nodal impulse may coincide with a premature beat in the left ventricle. It is not probable, however, that this would occur so frequently.

We suggest another explanation. The ectopic beats in the second tracing (Fig. 2) are due to an escape mechanism, mostly of nodal origin. The interval to the preceding QRS is always excessively long, mostly due to blocked P waves. Obviously, the disturbance of conduction, resulting in left bundle branch block, is functional. If the heart rate is within normal range, the delayed refractory period of the left bundle branch produces intraventricular block. If the heart rate is very slow, the recovery of the left bundle branch is more complete, so that the next following beat shows a much shorter QRS interval with a more normal QRS contour. This mechanism of functional intraventricular block is known.[2,3] The variation of the contour in several ectopic beats might be explained by a different site of impulse formation; the P–R intervals vary somewhat; no P waves are discernible in several ectopic beats. In Figure 2 the presence of a type of coronary insufficiency is shown only in the ectopic beats of the chest leads and not in the limb leads. This phenomenon is not rare in anterior wall infarction, and the same explanation holds obviously for the ectopic beats in our case as for the regular beats in other cases. However, in the first tracing, one ectopic beat in Lead 3 (Fig. 1*c*) shows the contour of coronary insufficiency. The fact that the ectopic beats in Lead 3 of the second electrocardiogram do not reveal these features, is possibly due to partial recovery of this particular lesion. The appearance of the infarct or coronary insufficiency pattern only in the ectopic beats, is obviously explained by the more normal spread of the impulse through the ventricles. The QRS interval of the ectopic beats including those with the infarct pattern in Lead CF_2 and of Type 1 in Lead CF_4 is shorter than in the regular beats. The different shape of the Type 2 ectopic beats is obviously due to a different focus of impulse formation. Type 2 also shows the contour of coronary insufficiency (deep Q and T inversion), but the QRS interval is about the same as in the regular beats. Since they are preceded by a long R–R interval, sufficient to restore the conduction time of the left bundle branch, it could be possible that the prolonged QRS interval in these beats (Type 2) has nothing to do with the original left bundle branch block of the regular beats, but is due to the site of impulse formation, which is obviously lower in Type 2 than in Type 1. Obviously, the mechanism of the phenomenon in the first electrocardiogram (Fig. 1) is different. Here no P waves are discernible, and the QRS interval is not shorter than that of the regular beats. It is possible that they are of ventricular origin, but the broad QRS interval is not easily compatible with mechanism *a*. No escape mechanism is involved, the beats are undoubtedly premature. While we cannot offer a satisfactory explanation for the phenomenon in the first electrocardiogram (Fig. 1), we wish to call attention to a fact which obviously is of importance. The interval between the preceding QRS and both premature beats in Lead CF_2, which show the phenomenon, is short (0.6 second), but the

R–R interval between the last 2 beats immediately before the premature beat is excessively long (1.24 seconds), longer than any other R–R intervals, and due to a premature nodal beat (third beat before the premature ventricular beat) with compensatory pause. Obviously, this combination was necessary to produce the phenomenon. In Lead 3 the same sequence: premature nodal beat, compensatory pause (R–R interval 1.24 seconds), premature ventricular beat with coronary insufficiency pattern, occurs as in Lead CF_2. A certain proof for this assumption is an ectopic nodal beat in the same lead (third beat, Fig. 1*d*), with smaller QRS interval, normal QRS contour and without the coronary insufficiency pattern. The R–R interval of the preceding regular beats is not prolonged (0.96 second).

Summary. In a case of left bundle branch block, premature ventricular beats in Lead 3 and CF_2 in the first electrocardiogram and nodal escape beats in Leads CF_2 and CF_4 of the second electrocardiogram, taken 1 day later, revealed the presence of acute coronary insufficiency, probably infarction, which was obscured by the intraventricular block in the regular beats. There was an evolution of the inverted T waves in the ectopic beats of CF_2 from the first to the second electrocardiogram. Multiple ectopic beats, due to nodal escape, in the limb leads show a shortening of the QRS intervals to normal limits and a normal QRS contour. The possible mechanism is discussed. Since the mechanism producing the ectopic beats varied, it can be concluded that the pattern of myocardial infarct or coronary insufficiency may be revealed in ectopic beats in the presence of intraventricular block, to a certain degree independent of the mechanism producing the ectopic beats.

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LARGE INTERAURICULAR SEPTAL DEFECT WITH PARTICULAR REFERENCE TO DIAGNOSIS AND LONGEVITY

Report of 2 New Cases

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Workers in the field of cardiovascular disease, particularly those interested in congenital defects, have learned during the past decade that one of the important and relatively common congenital anomalies, not previously recognized except in rare instances, is a large interauricular septal defect (I.A.S.D.). Of especial significance is the fact

that the clinical diagnosis is now possible in most cases, and yet that such a diagnosis may be a surprising discovery in a patient who has reached middle age in a fair state of health such as happened in 2 of our own cases. This fact recently excited our interest anew in the subject.

Only certain of the interauricular septal defects, referred to by anatomist and pathologist, are thought to be clinically important. Therefore, a few words are devoted herewith to the presentation of the clinical concept of this developmental defect. By I.A.S.D., as it concerns the clinician, is meant an aperture of 1 cm. or more in the interauricular septum.[15] Thus, only a small percentage of autopsied cases presenting an I.A.S.D. fall into this clinical classification; the larger percentage of lesser defects are of only anatomic and academic interest. Likewise, since the foramen ovale may not normally close before the 8th month of age,[15] such an opening found in the age group under 1 year is not regarded as clinically significant. There is much confusion in the medical literature as to the exact anatomic location of an interauricular defect. For this reason, it is often impossible to know in what part of the interauricular septum an aperture presents. Since, in the future, clinical correlation with the anatomic location of an I.A.S.D. may be demonstrated, writers on this subject had best use descriptive terminology in localizing the defect until that time when a universal and simplified embryologic classification has been devised. For example, to state that an aperture is present at the upper, middle, or lower part of the interauricular septum, meaning by "lower" that part adjacent to the ventricle, is to localize the defect clearly, no matter what the embryologic origin may be.

In 1934, Roesler[19] reviewed interauricular septal defects. He collected from the literature 62 autopsied cases. The youngest patient was 11 months and the oldest 75 years of age. He followed the classification of Costa.[4] Apparently defects measuring less than 1 cm. in diameter were not considered. Neither was this defect in combination with other congenital anomalies of the heart included in the series. The occurrence of this defect together with mitral stenosis was likewise summarized by McGinn and White[14] in 1933.

An analysis of the literature describing autopsied cases since Roesler's excellent review[19] has not been presented, although a valuable clinical paper by Bedford, Papp and Parkinson,[2] based on 53 personal cases (10 autopsied), has recently been published (1941). Since recognition of congenital interauricular septal defects clinically is more evident today, and inasmuch as certain new observations have been made by several authors, we have thought it worthwhile to bring the subject up to date. Thirty-one autopsied cases reported since 1933[1,3,5,6,7,11,12,13,16,17,20,21] (including our own Cases, 1 and 2) are clinically and pathologically analyzed. Eighteen of these cases, which ran an uncomplicated clinical course, are studied with particular reference to symptomatology and longevity. In certain instances figures from Roesler's series of 62 cases[19] are included for purposes of comparison. The 2 autopsied cases from this hospital are included to demonstrate an associated condition which may prove a not uncommon component

of the picture, and to emphasize the possibility of a fair length of life and considerable activity despite this defect.

Case Reports. CASE 1. G. S., a 43 year old native white woman had been affected since 8 years of age with gradually increasing dyspnea and cyanosis. At 35 years of age, she suffered from an attack of precordial pain which radiated down both arms; she was then hospitalized for 3 months. Similar pain, requiring hospitalization, recurred 2½ years later; there was Roentgen ray evidence of "thymus gland enlargement" for which deep Roentgen ray therapy was administered.

From the age of 39 up to the terminal illness, she attended the Out-Patient Department of the Massachusetts General Hospital at regular intervals. Her main symptoms were precordial pain (sometimes radiating down both arms and upward into the neck), usually preceded by nausea and often associated with a choking sensation, tightness in the chest, and marked cyanosis. Noteworthy physical examination findings included cyanosis, clubbing of the fingers, cardiac enlargement to the left, a precordial systolic murmur, and paralysis of the left vocal cord. The ECG showed marked right axis deviation. Roentgen ray examination revealed a "mediastinal mass" below the aortic arch and thickening of the lung hilar markings. She was completely digitalized with resultant improvement.

At 41 years of age, she was admitted to the M.G.H. as a patient on 2 occasions within a short period of time because of increased symptoms and a mild upper respiratory infection. Roentgen ray examination of the chest was described as again showing a "mediastinal mass" in the region of the main pulmonary artery. Physical examination revealed an accentuated pulmonary second sound, a blowing pulmonary systolic murmur with a corresponding thrill, and short systolic and presystolic apical murmurs.

On January 1, 1933, at 43 years of age, she was again admitted to the M.G.H. with symptoms of severe precordial pain, marked dyspnea, cyanosis, nausea, and vomiting. Physical examination findings were consistent with congestive heart failure complicated by pneumonia. Inspection revealed marked cyanosis, dyspnea, jugular vein distention, and pronounced clubbing of the fingers and toes. The blood pressure was recorded at 110 systolic and 70 diastolic. The pulse was small with a regular rate of 100 beats per minute. Respirations were labored. The left heart border extended to the anterior axillary line. There was a widely transmitted precordial systolic murmur. Moist râles were heard bilaterally over both lung fields; bronchial breathing and dullness were present over the left posterior chest. There was tenderness on palpation of the right upper abdominal quadrant. Laboratory studies were not remarkable. The complete blood count showed 11,000 W.B.C. and 6.5 million R.B.C. Urinalysis was negative. Treatment for cardiac failure was unsuccessful. The temperature remained elevated, up to 102° F. She complained of chest pain, most marked on the left, and vomited at frequent intervals. On January 15, 1933, her condition suddenly became worse and death supervened. A clinical diagnosis of (?)congenital heart disease (interauricular septal defect), (?)cor pulmonale, and bronchopneumonia was made.

Autopsy. Pertinent findings were confined chiefly to the heart, blood-vessels and lungs. The right ventricle was markedly hypertrophied and dilated, making up completely the anterior surface and apex of the heart. The right auricle was dilated. Enlargement of these chambers produced, respectively, enlargement to both left and right. An interauricular septal defect, measuring 3.5 cm. in diameter, was located just above the tricuspid valve. This defect was in the "exact location of the fossa ovale," and presented "in part, at least, a partial, patent foramen ovale." The left cardiac chambers were not enlarged. The valves, except for slight thickening along the free edge of the mitral valve, were normal in appearance. The pericardium was adherent to the root of the pulmonary artery. The artery itself and its branches were dilated and sclerotic. There was organized thrombosis of the left main pulmonary artery and its branches.

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The lungs showed pulmonary edema and infarction in the left lower lobe. Other necropsy findings consisted of healed bilateral apical pulmonary tuberculosis, pulmonary osteo-arthropathy of the fingers and toes, and slight aortic, coronary, and renal arteriosclerosis.

Comment on Case 1. That symptoms are not necessarily seriously disabling, and that an existent I.A.S.D. after onset of symptoms is compatible with a considerable length of life, is evident in the case of this patient who suffered from mild dyspnea for 35 years. The correct clinical diagnosis, questioned late in the course of the illness, was based upon the presence of chronic and marked right heart enlargement confirmed by Roentgen ray examination and ECG and in the absence of evidence pointing toward better explanations. The finding of a patent and unprotected foramen ovale at autopsy qualifies the statement of Bedford, Papp, and Parkinson,[2] that a patent foramen ovale "is clinically silent except that, when distended by increased auricular pressure ('widely patent'), it can give rise to terminal cyanosis and paradoxical embolism."

Left recurrent laryngeal nerve paralysis, present in this patient, was undoubtedly due to compression of the nerve between the dilated pulmonary artery and arch of the aorta, as recently suggested by Erlanger and Levine[6] in a report of 2 clinically studied cases.

A chronic cor pulmonale secondary to pulmonary endarteritis obliterans (with an incidental auricular septal defect) was thought to be a strong possibility during life, but was not confirmed postmortem; the pulmonary vascular changes were evidently secondary to the pulmonary hypertension due to the overloading of the lungs with blood and were not a primary condition.

CASE 2. J. P., a 59 year old native white woman had suffered from mild exertional dyspnea since early childhood. She married, had 3 children, and lived a full and active adult life up to the age of 45. At that time she suffered temporarily from a "nervous breakdown." She recovered from this episode and felt quite well until the age of 53 when she began to be bothered by sinus trouble and family worries. She was helped some by wintering in Florida.

In the spring of 1936, at 55 years of age, she complained of recent increased exertional dyspnea, palpitation, exhaustion, faintness on climbing stairs, and left chest discomfort. At that time physical examination revealed rather marked enlargement of the heart to the left and accentuated pulmonary second sound. There were no murmurs. The blood pressure was 115 systolic and 80 diastolic. The pulse was regular at 90 beats per minute. The ECG showed considerable right axis deviation with inverted T waves in Leads 2 and 3 and large P waves in Lead 2. Roentgen examination confirmed the percussion evidence of cardiac enlargement and, in addition, revealed prominence in the region of the pulmonary artery, an increase in hilar shadows and pulsations and left auricular enlargement. A diagnosis of an I.A.S.D. and neurocirculatory asthenia, together with climacteric symptoms, was made to explain the total picture. She gained no relief from her symptoms by digitalis, to which she was hypersensitive. However, reassurance and rest away from home were of benefit. Her course was followed closely with frequent physical examinations and laboratory check-up. A precordial systolic murmur developed within a year, her dyspnea steadily increased, and 6 months later cyanosis of the cheeks and tongue became apparent. Her circulatory condition remained stationary for several months except for the development of extrasystoles and

occasional fainting spells. In September, 1940, at 59 years of age, she felt much worse with a cold, anorexia, bouts of paroxysmal tachycardia, aud a sensation of "needles in the feet." Two months later, in November, 1940, she expired after a chill and fever and a few hours of suddenly increased dyspnea and cyanosis. A clinical diagnosis was made of pneumonia complicating a congenital interauricular septal defect.

Autopsy (restricted to heart and lungs). The heart weighed 475 gm. The right ventricle was markedly enlarged by hypertrophy and dilatation, making up the entire anterior surface and left border of the heart. The right auricle and pulmonary arteries were dilated. An open I.A.S.D., measuring 3 cm. in diameter, was noted. The mitral valve edge was thickened and the chordæ tendineæ were markedly shortened and thickened; the other valves were normal. Examination of the lungs revealed pneumonia in the stage of red hepatization involving a portion of the right lower lobe. Microscopic examination of the lungs revealed dilated pulmonary arteries, many showing medial hypertrophy; a large number of the smaller vessels showed marked intimal proliferation. There was evidence of generalized pulmonary congestion.

Comment on Case 2. As in Case 1, a fair length of life with little or no serious disability was demonstrated in a 59 year old woman affected with a symptomatic I.A.S.D. for years. Dyspnea was an early and prominent symptom. Careful clinical study failed to reveal the mitral valve deformity which was found at autopsy. The correct clinical diagnosis of an I.A.S.D. was made on the basis of long-standing mild symptoms without early cyanosis, together with physical examination, and Roentgen ray and ECG findings indicative of primary right heart embarrassment.

Date of Series Analyzed. The frequency of an I.A.S.D., as compared with other congenital cardiovascular lesions, is high. At the Mayo Clinic,[9] 87 of 8134 cases (1.05%) examined postmortem showed major cardiovascular anomalies. One-quarter of these, 21 (or 0.25% of all the cases) presented an I.A.S.D. measuring 1 cm. or more in diameter; the next most common anomaly was coarctation of the aorta, totaling 16 (0.19%); next in order of frequency were cases presenting an excess of pulmonary cusps. Autopsy surveys at other institutions have likewise resulted in the conclusion that interauricular septal defects rank as among the commonest of all congenital cardiovascular defects.

The sex incidence of I.A.S.D. is not significant. In Roesler's series[19] females predominated, while in ours, males comprised a bare majority of 1. Nor does sex, in regard to physical activity and child-bearing[19] influence its clinical course.

As suggested by McGinn and White,[15] an I.A.S.D. of less than 1 cm. in no way manifests itself during life, and for all practical purposes should not be considered clinically significant. Rare exceptions to this rule are instances with small paradoxical emboli, which in 1 reported case[8] passed through a pencil-sized foramen ovale. Since 1933 only 2 cases past middle age have been reported who were without symptoms up to the time of death. One, with a defect measuring 0.8 cm., died at 77 of pancreatitis;[18] the other, possessing a 1.5 cm. defect, died at 59 years from complications which were secondary to paradoxical embolism.[17] Apparently then, most, if not all, defects which measure

over 1 cm. sooner or later express themselves clinically. The average age of death, which was 36 years in Roesler's cases and 37 years in the present series, is not influenced by size of the defect when greater than 1 cm. It is of interest, as will be emphasized later, that in cases with rheumatic valvulitis, longevity was not appreciably affected after adulthood was reached. This fact stresses the primary importance of defects, regardless of existing valvulitis, in relation to mortality. The oldest cases in Roesler's[19] and in our series were 75 and 68, respectively. Of the latter series 54% lived beyond 40 years of age, thus indicating a fair life expectancy despite this lesion.

The symptoms accompanying I.A.S.D. cases, as explained by Roesler,[19] McGinn and White,[15] Bedford, Papp, and Parkinson,[2] as well as others, arise primarily from the increased blood volume in the pulmonary circuit, which results from backward blood flow through the opening between the left and right auricles and reduces the air space in the lungs. Therefore, as might be expected, the earliest symptom in 15 of 18 carefully studied cases was exertional dyspnea. Of the remaining 3 cases, 2 were without symptoms; [11,17] and 1, with heart block, suffered from fainting spells prior to the onset of dyspnea.[5] This suggests that dyspnea as an early symptom occurs in nearly 100% of these cases. Other symptoms were not necessarily related to the heart and circulation, except as they occurred terminally due to frank right heart failure. From the onset of dyspnea in these cases the average additional span of life was 14 years, ranging from 1 to 35 years. The dyspnea was, as a rule, mild, only slightly incapacitating, and usually existed without change for years before terminal heart failure set in. As a matter of fact, this early symptom was likely to be so benign that the physician was rarely consulted until late in the course of illness. The average survival after the onset of dyspnea, in 10 cases with associated mitral stenosis, was 13 years, as compared to 14 years in 5 cases where the septal defect occurred alone. The latter fact implies that the clinical course of adults with this defect is not significantly altered by the coëxistence of rheumatic heart disease.

Physical examination *per se*, except for the evidence it presents of right heart involvement, offers little or no assistance in the diagnosis of an I.A.S.D. However, together with a past history and in conjunction with other findings, it may assume importance. Since 53.8% of 93 cases included in Roesler's[19] and the present series showed mitral stenosis at autopsy, it is apparent that such a coëxisting valve lesion should be suspected rather than rejected in every case. Cyanosis occurred in 8 of our 31 cases. It developed early in 1 instance, was a terminal finding in 3, and in the remaining 4 cases was associated with frank heart failure. Cyanosis, therefore, is usually neither an early nor a consistent finding. Murmurs were commonly heard over the precordium. They were systolic, varied in intensity and pitch, were most commonly located at the 3rd or 4th left intercostal space parasternally, and were usually not accompanied by a thrill. The murmurs were not very loud, as a rule, and could easily be considered physiologic and so of no significance. The size of the defect and the degree of

cardiac failure in most instances bore no definite relationship to the characteristics of the murmur. It is likely that a certain percentage of these murmurs was due to dilatation of the pulmonary artery, since an I.A.S.D. has never been proved *per se* to be the source of a systolic murmur. As pointed out by some authorities, a murmur produced by the defect *per se* should logically be presystolic in time; yet in only 2 of 31 patients, was this said to have been the case.

Clinical evidence for mitral valve deformity does not compare favorably with its high autopsy incidence. In our series, 19 of 31 (62%) autopsied cases showed mitral stenosis, and only 9 of these were recognized clinically. Bedford, Papp, and Parkinson[2] found mitral stenosis in 4 of 10 autopsies, yet they report its presence in only 4 of 43 clinically studied cases. This discrepancy ("silent mitral stenosis") may be due to the two-directional passage of blood (from the left to the right auricle as well as through a stenosed mitral orifice), which results in a reduction in blood flow through the mitral opening to a degree less than is compatible with production of an audible murmur. Therefore, just as an existing mitral stenotic murmur does not rule out an auricular septal defect, neither does its absence (along with evidence favoring a septal defect) greatly decrease the likelihood of mitral stenosis. Arrhythmias, in the form of auricular fibrillation and flutter, were reported in 7 of our 31 cases, and, in every instance, were associated with mitral stenosis.

The correct clinical diagnosis of an I.A.S.D. is being made with increasing frequency. Its clinical recognition in but 1 of 62 cases up to 1934 (Roesler),[19] has since increased to 14 in 31 cases (present series). The latter more desirable and encouraging figure has undoubtedly resulted from the recent, more frequent recognition by Roentgen ray and ECG examination of primary right heart involvement. Such Roentgen ray findings observed are enlargement of the right ventricle and auricle, prominence of the pulmonary arc, and increased hilar markings, especially on the right (due to dilatation of the main pulmonary artery branches). Another finding, less often present but characteristic of such a defect, is an increase in hilar pulsations, the "hilar dance."

A high percentage of these cases show right axis deviation electrocardiographically. A majority of Roesler's series[19] presented slight right axis deviation. It was commonly encountered in Bedford, Papp, and Parkinson's[2] cases. In the present series of 31 cases it was mentioned as moderate or marked in 15 instances, including our 2 M.G.H. case reports. The ECG is very helpful and confirmatory.

In the future a more certain and exact diagnosis in a far greater percentage of cases will be forthcoming when roentgenologic and electrocardiographic evidence of pure right heart disease is correlated with other clinical findings. Radiographically, the picture observed of right heart enlargement does not appear to be altered by coëxistent mitral stenosis since, as already mentioned, the left auricle retains its normal size. However, an identical Roentgen ray picture of right heart embarrassment is displayed in certain extracardiac pulmonary con-

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ditions such as pulmonary arteriolar disease. At this point, both the history and physical findings must be referred to in the differential diagnosis. In pulmonary artery disease, symptoms and physical examination and Roentgen ray findings parallel and approach each other in degree of severity; cyanosis occurs early and is a prominent and constant finding; after the onset of symptoms, the disease is often rapidly disabling and terminates fatally. In the congenital heart cases, on the other hand, the symptoms are strikingly mild in contrast with the rather marked evidence of cardiac involvement by physical examination, Roentgen ray study, and ECG; cyanosis, if present, is inconstant and usually makes its appearance late; dyspnea is an early and outstanding symptom and most often exists as the sole manifestation of trouble for years before the appearance of terminal frank cardiac failure. Recent reports on diodrast visualization of the heart and great vessels are encouraging from the standpoint of localization and differentiation of obscure acquired and congenital cardiovascular conditions including I.A.S.D.[22]

A majority of these cases die in congestive failure. Complications, resulting in death, occurred in only 5 of 18 selected cases. Only 1 patient developed subacute bacterial endocarditis;[2] another died as a result of paradoxical embolism following pulmonary infection;[17] 2 developed pneumonia[2 and our Case 2], and 1 patient bled to death from a ruptured varix.[11] There is, therefore, relative freedom from serious complications in this condition as contrasted with a majority of other congenital cardiovascular defects. Three instances of chronic pericarditis together with rheumatic endocarditis have been reported.[1,3] However, although the incidence of the latter is high, it has not been shown that these conditions are either directly or indirectly related to the underlying septal defect. They are, therefore, not regarded as complications, although it is quite possible *vice versa* that mitral stenosis by obstructing the blood flow may make a small interauricular defect much larger.

The pathologic physiology of an I.A.S.D. has been adequately reviewed by others as well as summarized in the preceding discussion. The heart has been adequately studied at autopsy. However, such has not been the case with respect to the pulmonary vascular system. It is of interest in this regard that pulmonary arteriosclerosis was present in both of our cases, whereas such has seldom been mentioned by others. More careful microscopic study of the lungs may aid in explaining the somewhat inconstant and variable existence of cyanosis in these cases. It is readily conceivable that early cyanosis, occasionally met with, may be the direct consequence of long-standing diffuse pulmonary arteriolar sclerosis or to complicating pulmonary thrombosis.

Summary. Interauricular septal defects which measure 1 cm. or more in diameter in individuals over 8 months of age are of clinical significance, and occur more frequently than do other congenital cardiovascular anomalies. Lesser defects are silent except in rare instances where they may permit the passage of small emboli from the right to the left auricle.

To avoid confusion as to the location of an I.A.S.D., the suggestion is offered that it be described as being situated in the upper, middle or lower portion of the interauricular septum.

A clinical analysis is presented of comparative studies in 62 autopsied I.A.S.D. cases up to 1934 (collected by Roesler) with 31 autopsied I.A.S.D. cases collected since that date. There appears to be no definite sex preference. The size of the lesion beyond 1 cm. does not influence its symptomatic course or the longevity. Complicating mitral stenosis, except for occasionally associated auricular flutter and fibrillation, does not alter the picture after adulthood is reached. A majority of cases is only mildly disabled from dyspnea and may withstand the ordinary physical and mental wear and tear accompanying active life for years before succumbing to frank right heart failure. The average age of death lies between 36 and 37 years, and over 50% of persons live beyond 40 years of age. Not uncommonly, individuals may pass the middle age mark without ill effects from this lesion, as demonstrated by Case 2. Complications, other than congestive heart failure, which is at times associated with terminal pneumonia, are conspicuous by their rarity. Only 1 case complicated by subacute bacterial endocarditis has been reported.

It is conceivable that secondary pulmonary arteriolar disease may develop in certain instances and be responsible for decreasing longevity. Pulmonary vascular lesions (sclerosis and thrombosis) were noted at autopsy in our 2 cases. In the future, more careful microscopic examination of the pulmonary vascular bed should be accomplished.

The clinical recognition of I.A.S.D. cases has risen markedly in the past decade. A clinical diagnosis of nearly 50% (14 of 31 cases) has been made since 1933, whereas previously only 1 in 62 cases was so diagnosed though considered in 4 other cases. Roentgen ray investigation, electrocardiography, and a recognition of primary right heart involvement has been chiefly responsible for the recent percentage increase in diagnosis.

A further step in the recognition of these cases will be possible if Roentgen ray and ECG criteria are evaluated in lieu of certain associated symptoms and signs favoring an interauricular septal defect over pulmonary arteriolar disease as a cause for right heart embarrassment. In the latter instance, cyanosis is an early constant sign, longevity subsequent to the development of symptoms is short, and physical and Roentgen ray findings parallel the clinical course. In the former, mild dyspnea, usually without cyanosis, is an early and outstanding manifestation, and there is little or no disability for several years despite physical, Roentgen ray, and sometimes ECG findings indicative of rather marked right heart involvement. With these differentiating points in mind, it is believed that the diagnosis in the future will become possible in a much higher percentage of cases.

Left auricular pressure is apparently relieved by the passage of blood through an I.A.S.D. opening to the extent that there is little or no resultant left auricular enlargement despite coëxistent mitral stenosis. The Roentgen ray picture remains that of pure right heart

involvement. Therefore, mitral stenosis should offer no barrier to the diagnosis of a coëxisting defect. On the other hand an I.A.S.D., by affecting a reduction in the left auricular pressure, frequently results in disappearance of the mitral diastolic murmur as well as of left auricular enlargement in cases with mitral stenosis, and thus conceals the latter lesion. This fact is borne out by the discovery of coëxisting mitral stenosis in 19 of 31 autopsies in contrast to its clinical recognition in only 9 of these cases.

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DEVELOPMENTS IN ARTHRITIS*

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The problem of the arthritides is entering a new phase of development. Adumbration of the ultimate nature of the problem may be in sight. This is not to state that finality of detail can now be forthcoming. It is possible, however, to perceive new relations within the problem, and to offer added justification for certain therapeutic measures whose availability and value have not hitherto had sufficient recognition.

In the minds of many practitioners recent pronouncements[2,17] have left therapy of the arthritides in a confused and negative phase. In order to clarify this situation and indicate the rationale of the therapeutic approach, now developing, it will be useful to consider first the

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status of certain concepts which have long dominated the field and are still influential.

Origination in this country of the doctrine of focal infection near the turn of the century resulted in early extension of it to arthritic diseases with many beneficial results. Recognition of this relationship led to application of the apparent therapeutic corollary to it; namely, the use of vaccines. Contemporaneously, attention then extended to the use of non-specific protein and a host of cognate injections and measures, depending upon superficial or systemic reactions of greater or less severity. Throughout all of this period, which has lasted about 40 years, the dominant concept underlying the problem, at least of atrophic or rheumatoid arthritis, was infection, focal or otherwise. The chief approach to study of the disease was bacteriologic, and out of the experiences thus acquired grew some significant observations, such as those concerning sensitivity and agglutination and precipitin reactions in rheumatic disease.[3]

Establishment of atrophic arthritis as primarily a bacterial disease has not been possible, however, in spite of intensive and extensive efforts to this end.

With the passage of years, failures inherent in overemphasis upon focal infection and vaccines engendered skepticism and finally disapproval of them as significant factors in the treatment of arthritics. Indeed, in some quarters focal infection is now completely in the discard, even as a contributory factor to the arthritic syndrome, and there is grave danger that opinion will swing so far in this iconoclastic direction as to deny to arthritics advantages resulting from dispassionate evaluation of it. There will be the less excuse for such overaction, in that, shortly after the last war the writer and his associates[10,11] pointed out that infection, although important, could not be regarded as the basic cause of the problem and that many deviations of physiology deserved equal and, indeed, greater attention.

Thus, the clinician, the general practitioner in particular, is left at present with virtual elimination of the premises upon which he thought the problem rested and has little more than heat, massage, anodynes and, the "dernier cri" of the day, gold, with which to approach treatment of arthritics. It is therefore a purpose of the present article to show where new premises can be sought and to integrate new as well as some old factors into a brief but rational outline of therapy.

In 1928 the American Committee for the Control of Rheumatism expressed its belief that arthritis is a generalized disease with joint manifestations and is not primarily a disease of joints. This pronouncement has had general acceptance, but there has been relatively little inquiry as to the nature of the "generalized" process or processes concerned. Over a period of many years, however, there has grown up a considerable body of clinical evidence to suggest that disturbances in the great systems of the body, meaning chiefly the nervous, vascular, hemopoietic, and gastro-intestinal systems, are caught up in the disease, or basically underlie it, or both. Of these the deviations or

dislocations occurring in the nervous system are among the most graphic. In this connection it is common knowledge that some of the manifestations of the nervous system are mediated through the endocrine chain.

Some cases of arthritis are recognizably related to certain endocrine functions, especially gonadal. "Climacteric arthritis"[5] and "arthritis of the menopause" which have been encountered in the literature since 1855 are familiar designations. The temporarily beneficial influence of pregnancy upon the arthritic woman has also become more widely appreciated and the exacerbating effect of menstruation is known even to the laity. These several influences have usually been regarded, however, as contributory or aggravating rather than as reflecting a background of etiologic significance. This limited point of view is clearly indicated by the fact that, although the above relationships have been recognized for 50 years or more, research and therapeutic experimentation in arthritis have been during that period predominantly within the bacteriologic field.

The increasing availability and use of estrogenic substances within the past 6 to 8 years have served to strengthen the suspicion that certain varieties of arthritis derive from some imbalance of the gonodal hormones. This view has apparently been easy of acceptance for hypertrophic or osteo-arthritis which has been widely designated as a "degenerative" disease, but less easy for atrophic or rheumatoid arthritis which has been equally widely regarded as basically referable to infection.

Impressed by the potential importance of the relationships just mentioned, within the neuro-endocrine systems, to both great types of arthritis, atrophic and hypertrophic, the writer, in conjunction with C. W. Scull, endeavored recently to integrate known and hypothetical considerations, germane to the above field, in the form of a chart or diagram, having for its aim a better visualization of the arthritic problem as a whole.[12] It is recognized that such an ambitious attempt must fall short of its goal and reflect inaccuracies. It is also recognized, however, that most of the premises on which it is based reflect accepted physiologic dictum.

Development of the concept of psychosomatic medicine in the mind of the profession at large will perhaps prepare some readers to entertain more sympathetically than they otherwise might the considerations here advanced.

There is significant evidence for the view that the 2 great groups of the arthritides, atrophic and hypertrophic, together with certain other aspects of rheumatism, are at least partly referable to imbalance within the neuro-endocrine chain. There is no opportunity here to review this evidence in full; but, to illustrate the general principle under discussion, the following paragraph from the chart and publication referred to may be quoted. "Stimuli or factors such as heredity, physical activity, nutritive defects, infection, trauma and exposure may be conceived as impinging on a central mechanism. The factors comprising this mechanism are the great systems of the body; inter-

TABLE 1.—POSSIBLE RÔLE OF PRECIPITATING FACTORS ACTING SINGLY OR IN COMBINATION, IN PRODUCING SYMPTOMS OF CHRONIC RHEUMATIC DISORDERS THROUGH THE MEDIATION OF "CENTRAL FACTORS"

Precipitating or sustaining factors	Components and functions of neuro-endocrine system affected	Symptom-complex resulting in the arthritic	Type of arthritis involved
Infection, toxemia, hereditary imbalance, physiologic "draft," "starvation," vitamin deficiency	*Hypo*function of the *adrenotropic* factor of the pituitary	Increased susceptibility to infection, toxins, histamine	A and H
	or		
	Adrenal cortex	Asthenia	A
		Fatigue	A and H
		Hypotension	A
		Low BMR	A and H
		Caries	A and H
	*Hypo*function of the *growth* factor of the pituitary	Asthenic build	A
	or	Decreased capacity for protein synthesis	A and H
		Secondary anemia	
		Demineralization	A
	*Hyper*function of the *growth* factor of the pituitary	Calcification of cartilage	H
		Osteophytes	H
		Phalangeal enlargement	H
		Paresthesia	
		Megalocolon	H
		Sthenic build	H
Menopause	*Hypo*function of the *thyrotropic* factor of the pituitary	Low BMR	A and H
	or	"Dry" skin	H
	Thyroid		
	*Hyper*function of the *thyrotropic* factor of the pituitary	High BMR	
	or		
	Thyroid		
	*Hypo*function of the *gonadotropic* factor of the pituitary	Emotional instability	
		Sweating	
	or	"Flashes"	
	Gonads	Fatigue	
		Vasomotor instability	
		Arthralgia	A and H
		Headache	
		Hypertension	
Pregnancy	*Hyper*function of the *gonadotropic* factor of the pituitary	Relief of symptoms	A
	or		
	Gonads		
	*Hypo*vasopressor function of the posterior pituitary	Low blood pressure, decreased peristalsis	A and H
	*Hyper*vasopressor function of the posterior pituitary	Decreased skin capillary flow	
		Edema	
		Water retention	
Mechanical pressure by capsular distention, tissue swellings and bony overgrowth	*Nervous system*		
	Pain fibers	Pain	A and H
Nervous stress or strain from: worry, excessive activity, trauma, exposure to cold	*Vegetative nervous system*		
	Increased adrenergic response through epinephrine	Peripheral vasoconstrictions	A and H
		Hyperglycemia	
		Relaxation of gastro-intestinal tract	
	Overactivity of sympathetic system	Reduced resistance to fatigue—cold	
		Decreased BMR	A
		Poor regulation of body temperature	
	Increased cholinergic response through acetylcholine	Increased gastro-intestinal tone	
		Flushing	
		Palpitation	
		Sweating—general	
	Overactivity of parasympathetic system		

related, as they are known to be, through the central nervous and endocrine chains. Many of the objective phenomena of the rheumatoid syndrome can be seen to consist of phenomena which reflect, to some extent, normal activities of the systems concerned. It is, therefore, tempting to endeavor to relate some of these phenomena, as exhibited in disease, to under- or overaction of the systems or organs having comparable or parallel functions. No attempt to this end could be regarded with finality, but it is rather surprising to observe the extent to which such an hypothesis affords a working explanation of many otherwise apparently unrelated symptoms. The symptom-complex constituting rheumatic disease, regarded in this manner, may perhaps be better described as a Mesodermosis, since practically all of the tissues primarily involved are derived from the Mesoderm."

Since publication of this chart, there has appeared a report by Selye *et al.*[20] on the production of certain arthritic phenomena by injections of desoxycorticosterone into adrenalectomized and thyroidectomized, as well as normal rats. It is also to be noted that for some years Silberberg[21] has reported the induction of phenomena suggestive of hypertrophic arthritis following the administration of anterior pituitary to experimental animals. These several observations constitute a new experimental approach to the syndromes of arthritis and rheumatism, and help to lift these topics out of the restricted angle of contemplation in which they have long resided.

However suggestive the observations just recorded, the complexity of such experimentation will require time for exploration, not to say therapeutic fruition; if, indeed, this is to supervene. In the meantime, it is desirable that an attempt be made to correlate the various aspects of the problem under discussion with actual clinical experiences illustrative of them, with the aim of advancing therapy of living arthritics.

Effective therapy of arthritics requires a regimen of "total support" of the patient.[13] There are obviously 2 therapeutic aspects to total support; one, in general, removes from the field such accessible factors as make for or constitute worry, fatigue, faulty body mechanics, faulty nutrition and focal infection; the other seeks to provide constructive factors such as rest, correction of anemia, replacement therapy in the gastro-intestinal or endocrine system; tonic medication, sedation, physical therapy, and optimal nutrition. Obviously these objectives and measures overlap.

Recognition of the operation of neuro-endocrinous influences in the syndrome as a whole, and in a regimen of total support in particular, not only contributes to a rational concept of the nature of the disease but also serves to bring into better perspective a number of valuable therapeutic practices.

In illustration, the following cases, out of many, are cited, but they could hardly be regarded as more than sporadic examples unless scrutinized against the background of the probable explanation of them. In this light they reflect certain etiologic and therapeutic principles not often to be observed so free from complications to cloud the

issue. Grollman[5] remarks, "It is only the most striking changes (in neuro-endocrine relations) which draw our attention, while milder and more subtle effects escape notice."

Atrophic Arthritis. CASE 1. Dr. R. F., physician, aged 32, married, with 2 children, came to the office on December 23, 1941. He weighed 250 pounds, and was of the stocky, muscular type. He had played on a leading Eastern college football team and had since conducted a general practice, including maternity work. He was also engaged in defense war work.

His chief complaint was pain in the right knee, but the total distribution included the right shoulder, right ankle, and left wrist, together with generalized pain and stiffness in the morning. For the past 3 or 4 years he had had transient arthritis and migraine, especially after colds. The first serious attack of rheumatic nature followed a strep throat a month ago. There was a history of intestinal stasis. His father had had some rheumatism in the legs and his mother had been subject to migraine. The patient was himself subject to the allergic influence of a lucite wrist-watch band. The tonsils were out and he denied genito-urinary infection.

The physical examination was essentially negative except for the tongue, which was slightly coated. The patient could bend well but the lumbar spine was somewhat stiff. The gall bladder was negative to dye study and the basal metabolism was normal. There were reduplication and redundancy of the pelvic portion of the colon, a contour of spasticity and irritability, and moderate dilatation of the right half. The blood count was normal; the sedimentation was 20 mm. in one hour; the albumin-globulin ratio was 1.6; the cholesterol was 234; serum uric acid 4.5. Examination of the mouth showed a gingivitis of Class 2 (in a scale of 4); the nose and throat and genito-urinary tract were negative.

During the period of about 2 weeks within which the patient underwent the necessary examinations, he felt generalized pains in the feet, shoulders, knees, wrists, and elbows, which were worse. The patient said he felt "happiest" when under the influence of salicylates and had been taking 90 to 100 gr. of sodium salicylate a day, the usual prescription being sodium salicylate gr. 15, sodium iodide gr. 1; every 3 hours and once at night.

The indications in this case were clearly to reduce the activities of the patient, prescribe standardized periods of rest, light sedation, modify the diet as regards excess of carbohydrate since he was a large eater, cut down the salicylates, and attend to the gums.

The patient returned to his work carrying out instructions, and was next seen on June 16, 1942. He then said that he had felt very well after a month of treatment. About June 1 he had played golf and developed a lame back which cleared up after 1 week. The patient was spending 9 hours in bed at night and was taking a rest of 1 or 2 hours in the afternoon but no medication of any kind. At this period he said that he felt less "confident" than before the arthritis developed and had less "punch" but was not so fatigued. He was advised to cut down on coffee and to omit smoking. The patient said that he had been definitely surprised by the beneficial effect of rest and less work.

The patient was next heard from on May 23, 1943, at which time he wrote the following letter: "My arthritis has cleared up completely. Surprisingly enough to me, rest, as you suggested, seemed to be the answer. . . . ."

On November 7, 1943, he wrote as follows: "I recently applied for a Commission as Lieutenant in the Army. . . . . I have had no arthritis since I last communicated with you."

CASE 2. Dr. P. C., physician, aged 40, came to the office on November 11, 1941, complaining of pain in the right shoulder and general fatigue. The pain had begun suddenly 15 months previously, though 5 years before that the right wrist had been involved in the same way, and 10 to 11 years ago he had had rheumatic pain in the sternum. The condition as a whole had been worse in the last 5 months. The total distribution of disability was both

shoulders, both hips, both knees, lumbar-thoracic junction of the spine, and the left hand. The patient thought that the precipitating factors were fatigue and infection of a lingual tonsil in April, 1941. He regarded himself as a nervous individual and suffered from considerable insomnia because of pain in the shoulder and nocturia due to nervousness. He had been costive for 20 years.

He had had some dead teeth, had nerve deafness in the right ear; an appendectomy in 1910; and removal of tonsils and adenoids in 1920. In 1920 he had had an operation on the inferior right maxillary sinus; the left had been washed out 21 times. He complained somewhat of vertigo upon sudden change of position and also of tinnitus in the left ear. Nine years previously he had had Ménière's disease which lasted for a total of 5 years. He had also had a bilateral sphenoidectomy and removal of tonsil stumps in 1934.

Roentgen ray of the right shoulder showed a small calcified area in the supraspinatus tendon. The patient had attended a leading spa the previous summer but had been made worse. He had had intravenous injections of salicylates and iodine and had also had colchicine and short-wave diathermy. He had also been given Ertron, 50,000 units t.i.d. 6 months previously without benefit. Three months before being seen he had taken thiamin chloride, 10 mg. t.i.d., with increased appetite, but no effect upon the pain. He had not smoked for 10 years except occasionally. He was moderate in the use of alcohol. The physical examination was essentially negative and full blood studies showed no abnormalities except that the sedimentation rate was 60 mm. in 1 hour.

The nose and throat examination (November 21, 1941) revealed a pansinusitis which had cleared up but now showed reinfection and an acute ethmoidal involvement with empyema. The dental examination revealed a gingivitis of Class 2 and 3 (in a scale of 4). Genito-urinary examination was normal upon 2 occasions as was also the gall bladder under dye study, but the colon showed a contour of spasticity and irritability.

The patient volunteered the statement that eating much candy gave him arthritic pain the next day, but said that nevertheless he was a large eater of sweets.

He was cautioned about overwork, told to reduce his activities, to retire early, and to rest, regularly, 1 hour o.d. flat on his back. He was given phenobarbital, $\frac{1}{4}$ gr. q.d., tincture of nux vomica, mms. 3 t.i.d., and he was advised to hold down somewhat the dietary purines since the uric acid was 5 mg. per 100 cc.

The patient was seen in 2 weeks and volunteered that the sedation, rest and change of diet, especially the first two, had helped greatly.

On December 23, 1941 he reported that he had had baking and massage to the shoulder which was improved. No treatment had been given to the gums, sinuses or teeth. He said that he no longer ate candy and thought that quiet, rest and phenobarbital had helped most, stating, "I am getting better on next to nothing."

On January 20, 1942, he said that he had been doing well until the past week when he had had an attack of grippe and had felt pain in the hips and lumbosacral region. He had missed the daily rest of 1 hour for the previous week—"I was too busy, seeing 43 patients in one day." He was up at 9 A.M. and went to bed at 10.30 P.M., exhausted. Nothing had been done as yet about the teeth or other foci, and there had been no baking or massage to the shoulder recently but more motion and function were present. He had less sinusitis, was less costive and was less nervous. The blood pressure was 160/100.

On November 30, 1943 he had some stiffness in the hands, and realized that he should persevere in the original recommendations laid down, but was nevertheless carrying on a busy practice and regarded the advice again given him as having theoretical rather than necessitous significance. An ECG taken 1 month previously was normal. The patient was taking little or no medicine except, occasionally, phenobarbital, gr. $\frac{1}{4}$, extract belladonna, gr. $\frac{1}{6}$.

This case offers a clear-cut example of atrophic arthritis in its relatively early stages, in a busy practitioner, complicated by foci of infection, some

increase in blood pressure, an irritable nervous system and a condition of the gastro-intestinal tract verging on spastic colitis.

In spite of the above complications or contributory factors, some of which would have been universally regarded as the essential etiologic factors only a few years ago, this patient experienced a dramatic improvement on the basis of "physiologic" adjustments and was even able to carry on his practice without serious interruption. Good practice really required that the patient renounce most or all of his work, enter upon a programme of complete rest, care for the infection present, and generally conform to the recommendations set forth in Table 3. The case is chosen, however, to illustrate how influential the simplest of measures may be even though carried out with less than the recommended thoroughness. This experience is not to be regarded as justification for such laxity.

CASE 3. Mrs. L. E., aged 55, presented herself on January 31, 1939, with almost complete fibrous ankylosis of the fingers of the left hand due to atrophic arthritis. About the only useful motion left was a slight amount between the thumb and forefinger, and the hand resembled a fin. There were discomfort and angulation at the left elbow. The left shoulder, the knees and left sacro-iliac joint were also painful. She complained of paresthesias of the toes and of muscular twitching which frequently awakened her at night.

There were edema of the left hand and tenderness over the manubrium at the junction of the costal cartilage. The external malleoli were puffy; the left hip rotated with tenderness; there was some descent of the lumbar spine upon complete flexion of the left femur and there was tenderness at Poupart's ligament on the left and at the left iliac crest. There was also tenderness at the 7th cervical and 5th thoracic vertebræ. The throat was dry and glairy with a history of catarrh, and the nurse stated that the patient was very nervous and smoked from 1½ to 2 packs of cigarettes daily.

At the age of 11, the patient's knees would swell in winter as they did again at 14 after diphtheria antitoxin; during the past 3 winters she had also had stiff knees most of the time. Both sides of her family had had arthritis, and on her father's side there was psoriasis, which the patient also presented. There had been intestinal stasis for 22 years and many attacks of tonsillitis. Two infected teeth had been removed 4 or 5 years ago. The patient was physically fatigued. She was a large eater of rich foods and disliked greens and fruits. At one time she had been in bed for 3 weeks for a condition diagnosed as "colitis" and had had many "cures" abroad.

A year previous to admission she had had 2 attacks of vertigo. She had had a tonsillectomy some years before as well as an appendectomy and a repair operation. The removal of 2 teeth had helped the right arm and shoulder, although later she had had 8 injections of streptococcal vaccine. She had also had short-wave diathermy, general massage and colonic irrigations. At one recent period she took 5 grains of aspirin and ½ grain of codeine sulfate every 4 hours for 4 months. Of late the patient had been taking 30 grains of aspirin every 24 hours.

The significant laboratory findings were as follows: Basal metabolism minus 23; sedimentation rate 23 mm. in 1 hour, on a scale of which 12 mm. in 1 hour was the normal limit; cholesterol 270. There was a Class 2 gingivitis (in a scale of 4). The nose and throat showed evidences of previous inflammation in the sinuses, but were free from infection at the time of examination. The Roentgen ray showed a spastic colon, marked demineralization of the left hand, and a classic picture of atrophic or rheumatoid arthritis.

This patient, who had been ambulatory, was put to bed and kept there. She was given mild sedation together with gentle stimulation with tincture of nux vomica. She was given a diet high in protein, reasonably high in fats and somewhat restricted in concentrated carbohydrate foodstuffs. This diet was also high in vegetables and fruits which were usually put through a colander to avoid undue roughage. She was also given accessory vitamins and was required to stop all smoking. Heat and gentle effleurage were administered to the involved parts.

From the start she began to evince improvement as indicated by less tenderness, freer movement of the fingers, fuller extension and motion of the left elbow and also diminished pain and freer movement in the left shoulder.

After 3 weeks she was given Armour's thyroid extract, gr. 1/5 twice a day. It is to be noted, however, that she had made a definite advance before getting this and also that 20 years before, after a B.M.R. test, the patient had taken thyroid for some months.

The result in this case was that this patient made a complete recovery except for the destruction of cartilage and the fibrous ankylosis already present. She kept under sporadic observation and remained well for 2 years.

On September 28, 1943, this patient presented herself again, with a history of having fallen and suffered a Colles' fracture of the right arm. The fracture had been treated by an orthopedist who put the arm in a plaster cast. After 4 weeks the cast was removed and it was found that all of the fingers of the right hand had reached a condition closely resembling that presenting in the left hand, except for added tumefaction, edema, etc., on the fractured side. It was clear that the processes of atrophic arthritis in the hand were intense and were leading to complete incapacity of it. No prehensile motion was left except slight approximation of the forefinger and thumb. Several of the mid-joints of the fingers showed distinct tenderness upon lateral pressure.

Upon observing the condition of the right hand when the cast was removed, she consulted a well-known rheumatologist who advised her to undergo a course of gold salts. Having acquired some knowledge of arthritis through her previous experience, the patient believed that such a step would be unwise and did not enter upon it.

She had been leading an active life prior to the accident but was at once placed under conditions of restricted activity and enforced rest. The basal metabolism was still minus 25, the cholesterol was now 427 mg. per 100 ml., and the sedimentation rate was 53 mm. in 1 hour. The blood was otherwise negative. Physical therapy was begun in the form of baking and massage to the fractured hand and arm. She was again given mild sedation, gentle tonic stimulation and accessory vitamins. She was placed upon a diet balanced as before and from the start began to make significant progress. Consultation with Dr. Charles W. Dunn in respect to endocrine imbalance resulted in the conclusion that this patient was suffering from a long-standing anterior pituitary deficiency, and she was given: Anterior pituitary, gr. 1; Thyroxin 0.15 mg.; Calcium glycerophosphate, gr. 5 b.d. It was recognized that there is division of opinion as to the efficacy of anterior pituitary administered per orem.

By the latter part of April, 1944, the right hand had almost achieved the condition of the left, having lost nearly all of the excess tissue fluid. There had also been achieved some approximation of the first fingers and thumb on that side so that both hands now functioned in limited but almost identical manner. At this point the patient volunteered that notwithstanding her inability to use her hands normally, she felt happier and more serene than ever before in her life.

This case conveys important lessons. In the first place, upon the first admission the patient started to make a significant return to health without the intermediation of replacement therapy in spite of the fact that for years she had had a low metabolism and had once been given replacement therapy for it.

In the second place, after full clinical recovery from this episode, it is clear that some background for recrudescence of the arthritis was still present. The fracture, followed by the application of a cast, together with the fact that she had not been living her life as "physiologically" as she should, permitted the arthritic process again to become active. It is obvious that the treatment instituted for this fracture by means of a non-removable cast was faulty and open to major criticism. If the hand had been put in a removable cast and had been given baking, effleurage and, later, massage during the

period of incarceration, the fibrous ankylosis characteristic of atrophic arthritis would probably not have developed.

The addition of endocrine therapy contributed to the rapidity of later convalescence but was not the sole or determining factor in this. In fact, on April 26, 1944, the basal metabolism was still minus 25. It is of much interest to note that, in spite of a dosage of thyroxin beginning March 22, 1944, of 0.30 mg., and increasing on May 11, 1944, to 0.35 mg., a hormonal assay on May 30, 1944 (conducted in collaboration with Dr. A. E. Rakoff), showed the following multiple imbalance, representative of a severe postmenopausal state: Urinary gonadotropins in international units per 24 hours—more than 100 (markedly excessive); urinary estrogens in mouse units per 24 hours, 6 (diminished); urinary 17 ketosteroids—1.8 mg., equivalent androsterone per 24 hours (diminished). The high gonadotropic assay is not out of keeping with the clinical opinion of anterior pituitary deficiency, since it reflects only one of several activities. The relationships here concerned will be made the subject of a later contribution.

In sum, this case is, therefore, an outstanding example of the fact that atrophic arthritis may be accompanied, and was apparently induced in this instance, by imbalance of a clear-cut endocrine nature. To meet this deficiency the patient had in the past been given thyroid. When first seen, the thyroid had long been stopped and marked convalescence was then initiated even in the absence of thyroid medication. Full recovery ensued. The full cycle of arthritis of the hand, following fracture, was then repeated, again followed by recovery.

This experience illustrates the efficacy of the therapeutic principle of achieving better equilibrium in the major systems of the body and also presumably in the endocrine chain. Partial replacement therapy was later useful but was never pushed to the point of complete replacement.

Hypertrophic Arthritis. CASE 4. Mrs. Wm. M. S., aged 63, was admitted to the Hospital April 2, 1941. Her chief complaint was in the fingers, which showed the beginning formation of Heberden's nodes. The present illness dated from August 8, 1940 when she had had sulfanilamide for a severe tonsillar infection. This was followed by generalized rheumatic pains for which she was in bed for 6 weeks. She had also had a course of streptococcal vaccines and diathermy and had had more pain in the past 2 months. One brother had had rheumatic fever and 1 daughter was said to have had rheumatic fever at the age of 7. The patient had been very active in sociologic work. She was a rather large eater.

The physical examination was essentially negative except that the right kidney was palpable in the first degree, and the blood pressure was somewhat elevated. The blood, sedimentation rate and basal metabolism were normal. There was a Class 2 gingivitis (in a scale of 4). The cecum occupied a transverse position and the descending colon lacked haustration.

The patient was kept in bed and given gentle sedation while her case was being studied. From the start she made a marked advance and then experienced decreasing tenderness in the hands. She was then placed upon a well balanced ration to be described later, and local treatments were carried out upon the tonsils and gums. After 12 days in the hospital she returned to her home with strict injunctions to adhere to the regimen instituted at the hospital.

She was readmitted to the hospital for a "checkup" on June 24, 1942, at which time she had been free from arthritic symptoms since the previous admission. She had been too active in war work, however, and the blood pressure was too high, being 180/90. This patient was seen several times in the course of the subsequent year, at the end of which time she was still in excellent health. This case illustrates the fact that there may be no clear-cut evidence of endocrine deficiency as manifested by the basal metabolism,

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although the cholesterol at the time of the first admission was as high as 331. The relatively minor changes in this patient's way of living, imposing also some restraint upon her physical activities, relieved her of all symptoms.

CASE 5. Mrs. M. T., aged 65, entered the Hospital April 28, 1943, with definite evidences of hypertrophic arthritis, complaining chiefly of pain in the hips and thighs, especially the right. The hands showed Heberden's nodes. The duration of symptoms was about 14 years. The previous summer had been strenuous for the patient due to the illness of her husband, and the pain in the right thigh and hip had been so severe that in the spring of 1943 she had to spend 2 weeks in bed. The heart showed evidence of slight myocardial damage; there was tenderness of the vastus externus on the right. The right thigh flexed freely but on external rotation there was pain in the vastus externus. The same was true of the left thigh, though less so. There was pain in the left heel and she could bend only two-thirds of the normal range. She presented a slight degree of spasmus nutans of the head.

Roentgen rays showed narrowing of the joint fissure in both hips with moderately advanced hypertrophic changes in the sacro-iliac joints. There was well advanced hypertrophic arthritis involving the intertarsal joints, with a spur 3 to 4 cm. long on the left heel. There was an osteophyte on the articular surface of the right tibia with spur formation on the left.

There were a Class 2 gingivitis (in a scale of 4) and chronic tonsillitis with pus in the right tonsil. The blood was negative and the sedimentation and B.M.R. were normal.

Upon admission she was at once placed upon a regimen of complete confinement to bed, gentle sedation, and a well balanced but not "excessive" diet. Twelve days after admission she was much better; the legs had lost nearly all tenderness and the hands looked collapsed. Three days later an infected tooth was removed.

The immediately precipitating factors seemed to have been overactivity and nervous strain, complicated possibly by infection in the tonsils and mouth.

The patient returned home about a month after admission, greatly improved, with strict injunctions to follow rigidly the regimen instituted at the hospital. This she did, with the exception of periods when the illness of her husband required that she sacrifice herself in his behalf, and remained essentially free from discomfort, and able to carry on with efficiency, when last heard from in May, 1944.

This patient had been seen in 1931 and 1932 with comparable complaints, from which she made such a gratifying recovery that she was lost to observation for over 10 years. The treatment followed on those occasions was identical in principle with that described above. The evidence of hypertrophic arthritis in the hands had increased in the years which had elapsed but the patient volunteered that she had grown careless with her regimen. The last admission in 1943 is first cited because the picture of hypertrophic arthritis is more adequately illustrated.

This case reflects a clear-cut example of hypertrophic arthritis in which no specific evidence of endocrine deficiency was available and hence there was no clear indication for specific replacement therapy. There can be small doubt that the patient belonged in that group of cases referable to imbalance in the neuro-endocrine system, but achievement of the "equilibrium" discussed sufficed to inaugurate and maintain convalescence.

Some reflections of Cases 1 and 2 presented here are being encountered in the Armed Forces, at least in this country, and a similar situation was experienced in the last war. These cases present difficulties of diagnosis as to type and especially of disposition. They may present few Roentgen ray evidences and they stop short of the typical picture

of either atrophic arthritis or rheumatic fever. In the last war these cases were included in an extensive survey of arthritics in the army,[10] and it was found that many of them originated through "exposure" which constituted the etiologic factor in 60% of the whole series. It was also noted that five times more men recovered in the presence of focal infection than recovered after the removal of it. This experience brought sharply to mind the fact that elements other than infection must be at least contributory to the syndrome, although at that time it was regarded as heresy to question the etiologic rôle of infection. In 1941, Halliday[7] called attention to somewhat comparable cases which he termed psychosomatic rheumatism, and more recently Boland and Corr[1] have discussed the occurrence of certain types of rheumatic disability in the Army under the title of Psychogenic Rheumatism. The writer has seen many similar cases in the army hospitals of the present war and has been repeatedly questioned by medical officers as to proper classification of them. These cases obviously constitute in the Armed Forces a sort of laboratory experiment in the induction of arthritis. The factors bringing it on, at least in this country, are largely those also present, in principle, in civil life. However, in peacetime, few large bodies of young men are long subjected to comparable intensive strain, both physical and mental; a fact which doubtless accounts for the small numbers of these cases encountered in civilian clinics.

The striking figures from the last war revealing the high percentage recovery of the large group studied in the course of a few months after they had been invalided, is probably referable to recuperative processes operative along the general lines discussed in the present text. There has not, as yet, been enough experience in these cases to justify strong postulates regarding them, but it is probable, on the basis of such instances as form, in part, the substance of this article, that at least some cases developing in the Army need in principle the kind of therapy outlined above.

It is also possible that psychiatric examination of these individuals would throw light upon the situation as a whole.

In reviewing the above group of cases from civil life no great single deviation stands out in the congerie of influences operative, and the situation is rather one in which apparently minor deviations disturb normal physiologic relationships. Analogy to this can be seen in the field of nutrition, where partial avitaminoses may be induced by extraneous factors which exert an influence upon the conditions of the nutritional equilibrium rather than upon the amounts of vitamins *per se*. Experimental animals fed rations which are antiscorbutic, under resting conditions, will develop scurvy on the same diet if exercised. This is equally true of other vitamins and of other precipitating factors, such as infection, or a diet excessive in one of its constituents.

Some explanation is now available as to the *modus operandi* of certain steps which should be basic in the therapy of arthritis. Thus, there is subscription, among a few close students of the subject, to the view

that rest is prerequisite to successful treatment of the sick arthritic, but it is to be doubted whether this viewpoint often extends beyond injunctions to "take things easy," or that it actually requires that the patient stay in bed under a strictly balanced regimen. It is, furthermore, definitely clear that such practice has not extended widely among the profession as a whole, to the great cost of arthritics, especially in the early and formative stages of the disease.

A recent survey of the kinds of therapy practiced by physicians treating arthritics revealed that less than 11% prescribed rest. Many patients of the writer's series had been previously advised to keep moving their joints "even if it hurts, so that they will not get stiff." The issue involved here may be very confusing to both physician and patient. The greater mobility induced by movement and exercise is only temporary, due to the "hyper-physiology" and increased blood flow brought about, and results in added trauma and damage to the part. The postural exercises recommended to be taken even in bed (Tables 2 and 3) are carried out within sharp physiologic limitations and constitute a different issue.

TABLE 2.—CONDITIONED REST

1. Conditioned rest is not mere negation of activity; as such it could be harmful in many ways.
2. In rheumatoid or atrophic arthritis it may lead to ankylosis unless controlled.
3. Most patients undergoing rest should experience some form of physical therapy, postural exercise, or be allowed up for brief periods daily.
4. Properly conditioned rest, in bed—
   (*a*) promotes passage of tissue fluids into the vascular channels;
   (*b*) promotes opening of peripheral capillaries because of warmth induced by the bed clothes;
   (*c*) promotes relief from static strains incident to maintenance of the erect posture;
   (*d*) promotes relaxation of the nervous system;
   (*e*) allows ptosed organs to assume proper position and function;
   (*f*) reduces metabolic load;
   (*g*) permits settlement of metabolic deficiencies.

TABLE 3.—GENERAL ORDER OF TREATMENT

1. Rest, systemic as well as local
2. Psychic evaluation
3. Sedation and/or stimulation; *never opiates*
4. Optimal nutrition in a refined sense, including accessory vitamins if necessary
5. Proper gastro-intestinal function
6. Examination of the blood and body chemistry
7. Time for establishment of a general equilibrium
8. Psychic reëducation
9. Examination for foci of infection
10. Medication, such as iron, arsenic, nux vomica
11. Replacement therapy when indicated
12. Treatment of foci, conservatively
13. Use of physical therapy, conservatively—chiefly heat, gentle massage, postural exercise
14. Orthopedic help
15. Last, if at all, gold, vaccines, non-specific proteins.

Analysis of the influence of rest reveals that rest is more than mere negation of activity and is composed of constituent parts, each of which is a topic for scrutiny in itself. Some of these topics afford a "raison d'être" for the present contribution. In Table 2, setting

forth the components of rest just discussed, it will be observed that the several components specified reflect, in part, changes taking place in the vascular and nervous systems. Some of these changes can be observed clinically by anyone, and were made a goal in that therapeutic approach to treatment of the arthritic by the author and his associates which attempts to bring about a better equilibrium in the major systems of the body.[14] This goal still remains the clinical desideratum, and "en faute de mieux" in the way of specific accomplishment, is still to be sought. Particularly graphic, because early visible, is the diminution of the tissue edema, especially of the hands, which may ensue within a few days.[8,18,22]

The necessity for a period of recuperation can be observed in many conditions involving imbalance of the neuro-endocrine chain. Thus, exhaustion of the adrenals of experimental animals through exposure to heat or cold causes a demonstrable disappearance of osmic acid-reducing substances.[4,19] Infectious, toxic, or metabolic diseases cause a loss of lipoids and vacuolization of the cells. The characteristic doubly refractive substance of the cortex vanishes under conditions of exhaustion and increases under conditions of rest. Many other illustrations could be adduced.

To date, therapy in the endocrine field has been chiefly concerned with "replacement" therapy and less concerned with reëstablishment of normal relationships between the several links of the chain by means of decreasing the "load" so that dysfunctioning factors may operate within the limits of their normal potential. Full use is made of this principle in cardiovascular disease, for example, but scant use is made of it in arthritis. When practiced, however, a very few days may suffice, in some cases, to change the overall picture of acute, active arthritis to one of abatement. Clinical corroboration of the general viewpoint here discussed is to be seen in the adjuvant use of gentle sedation, free from any anodyne influence, and in the use of mild "tonic" stimulation. These apparently opposing influences are not incompatible. As regards sedation, it is difficult to say what phases of the cerebrospinal axis and endocrine chain are most usefully or "specifically" affected. In some cases, when first seen, the psyche may be unduly excited, but in others there may be the most reasoning calm. In nearly all, however, gentle sedation under conditions of bed rest may have surprising consequences. This statement is not to be interpreted as constituting a formal or isolated therapy of arthritis, but as an illustration of the extent to which basic factors within the neuro-endocrine system are open to favorable influence even though "replacement" therapy is not indicated or available.

The better equilibrium of and between the major systems of the body which the writer and his associates have frequently stressed, now appears as the "external" consequence, in part at least, of a better equilibrium of and between the component structures of the neuro-endocrine system. Such a concept advances measurably understanding of the clinical phenomena with which the practitioner who treats arthritis must deal. Under this interpretation, either great type of

arthritis can be seen, in part, as a series of sequential or related phenomena, expressive of known functions of the endocrine system which has, in some cases, exceeded, in others failed to achieve, its normal level of activity. No single major deviation seems to dominate the field and, at the outset, restoration of a balance under which the peripheral phenomena grow less or disappear is usually possible of demonstration.

The fact that later in the disease, when chronicity has supervened, such restitution is more difficult, should not be allowed to cloud the issue. Indeed, it not infrequently happens even in advanced cases that the same improved equilibrium can be achieved almost as easily. It is important to reiterate that control of such a situation cannot necessarily depend upon replacement therapy alone. Hyperactivity may also prevail and perhaps equally frequently.

The broad lesson taught by recital of the foregoing cases needs some further particularization. To discuss first hypertrophic or osteo-arthritis, it is clear from the cases cited by Hall and others,[6] as well as many in the writer's series, that "arthritis of the menopause" is amenable in a high percentage of instances to replacement therapy by means of estrogenic substances. The conclusion is unavoidable that a deficiency and imbalance in the endocrine field account essentially for the disease picture. It is equally clear that hypertrophic or osteo-arthritis, the pathologic name for "arthritis of the menopause," as illustrated in cases cited in the present text, is amenable to a therapeutic programme which centers around conditioned rest and correction of such physiologic burdens as may need adjustment, without resorting to any form of endocrine replacement therapy *per se*. The inference is equally inescapable in this second group cited that imbalance or deficiency accounts for the disease picture there also; certainly there is no justification for invoking another pathologic explanation for the same picture.

The corollary to this is that, even in the presence of a need for "replacement therapy," much the same results can be obtained by achieving an "equilibrium" between the several systems and endocrines concerned, even though replacement therapy *per se* be not administered. This is not to say that replacement therapy is to be omitted if indicated and available; it is to say, however, that even when it is available an "equilibrium" should equally be sought, since it is contributory to the same end and promotes better response to "specific" replacement.

Above and beyond these considerations, however, there is no assurance in this vexed field of the arthritides that we are dealing with single or specific deficiencies. The possibility must be entertained that several deficiencies exist or even, as just mentioned, that hyperactive states exist also. Indeed, such a condition of affairs is highly probable, and has been encountered in some cases of the writer's series as well as by other observers. Selye[20] concludes from his experimental work on animals that "the most prominent fact about the clinical syndrome of endocrine arthritis is that both hyperfunction

and hypofunction of several endocrine glands may elicit joint manifestations."

It is well recognized by students of endocrinology that the various endocrines bear active and often reciprocal relationships toward one another, such that dysfunction of one may have many and varied consequences elsewhere in the "chain." Without laboring further the possibilities involved here, it is plain that limitations to our knowledge of the number and kind of endocrinous dysfunctions, as well as limitations to the preparations available, justify emphasis upon any procedure which achieves the equilibrium above discussed. Indeed, such a course offers the only promise of bringing to bear influences upon a situation *so generic as to affect multiple imbalance.*

As already pointed out, the frequency with which such efforts meet with success is far from appreciated. They deserve wider use. Practiced rigidly in the way outlined, the therapy of arthritis teaches that the arthritic process is partly a reversible one, especially at the early stages, but to some extent also later in the disease, except for such gross pathologic changes as may have supervened.

Upon applying the principle of "achievement of equilibrium," just discussed, to *atrophic* or *rheumatoid* arthritis on the basis of the view that one is furthering a better balance within the neuro-endocrine chain and so affecting the bases of the disease, one is perhaps upon somewhat less secure ground. There is not, as yet, as much clinical evidence with which to incriminate the endocrine system in atrophic arthritis as in the case of the hypertrophic type. Nevertheless, evidence is not lacking as will be seen by reference to Table 1 and Case 3 (Mrs. E).

It is not justifiable as yet to say that atrophic arthritis stems chiefly out of a neuro-endocrine imbalance, but at the moment there appears to be no other explanation or hypothesis which so nearly accounts for the full picture.

In the present series, 3 cases of frank atrophic or rheumatoid arthritis have been selected, in 2 of which there was no clear-cut evidence of any single specific endocrine deficiency. There was consequently no clear indication for any specific replacement therapy. In the third case there was a lowered metabolic rate, and hormonal assay of the urine showed excessive production of one hormone and deficient production of two others. These several individuals were successfully treated upon much the same principle, *viz.*, that of making less significant such inadequacies as might exist by means of decreasing the load upon them. From the purely clinical standpoint this is a logical corollary to replacement therapy, albeit not specific for any one deficiency. That it works in selected cases admits of no question, and it is probably influential in most cases when exhibited. On the other side of the picture it seems probable, as mentioned, that at times at least, hyperactivity exists in arthritis somewhere along the endocrine chain, analogous to the influence of the anterior pituitary on hypertrophic arthritis. Obviously no "subtraction" therapy is possible here, but it is entirely reasonable to suppose, in view of the known close interrelations of the major endocrines to each other, that a better equilibrium

between all or most of them would be a step towards restoration of normal function. It is in this connection that gentle sedation may be influential.

Translated into practical terms, the above considerations require the establishment of a regimen which must be followed rigidly and literally. To this end Table 3 was prepared, setting forth the order in which the above therapeutic steps can usually best be taken.

Referring to Paragraph 3 of Table 3, the amount of sedation required by these subjects is usually very small, if exhibited in conjunction with complete bed rest; and, indeed, with the whole programme. As little as gr. $\frac{1}{4}$ phenobarbital, or some comparable sedative, q.i.d. will usually suffice, except perhaps on the first day or two. The fatigued state of which most arthritics complain will be greatly ameliorated in the same way by very small doses of tincture of nux vomica, as little as mm. 3, t.i.d.

By the term "optimal nutrition," Paragraph 4 of Table 3, is meant a diet which must vary with the individual but centers around an adequate though not excessive caloric intake, high protein content, ample "green" vegetables and fruits, ample fat and some restriction of the concentrated carbohydrate foodstuffs.[9,16,22] Again, the purpose in entering upon these details here is not to set forth a full therapy for chronic arthritis, which has been done elsewhere,[14,15,23] but to illustrate, in the light of the newer outlook upon the syndrome, the gratifying extent to which the simplest of procedures may initiate convalescence. Another reason for including Table 3 is to make clear that no single therapeutic measure is to be considered alone but only in conjunction with a broad-gauged and multi-faceted programme.

It is not to be supposed that the simple but effective foundation for further therapy, above discussed, will succeed equally well in all cases. Processes of recovery will usually be operative if given an opportunity but, obviously, the presence of massive infection, marked anemia, low plasma proteins, etc., may militate against recovery until corrected or improved. Clinical experience and sound judgment are as essential here as in any other major chapter of medicine, perhaps more than in most, as the brief discussion of the influences of rest and movement well illustrates. Mere titular familiarity with the physiologic aspects of rest, nutrition, exercise, physical therapy, etc., has wreaked havoc with hosts of arthritics. Anyone expecting a panacea in the physiologic approach discussed will be disappointed, and the object of emphasis upon it here is merely to make clear that such disturbances within the neuro-endocrine field as probably underlie the syndrome are often susceptible of correction by means of such an approach.

Another important corollary to the principle of "equilibration" of the arthritic derives from the unfortunate extent to which these sufferers are made the object of injections of various sorts, massive vitamin therapy and other more or less heroic measures. Although there is general agreement that procedures which elicit maximal reactions of the defense mechanisms of the body, such as fever, may have valuable consequences in certain disease states, such reactions have

not won routine acceptance for arthritics from critical students of the subject. Not only may these reactions fail to benefit the arthritic, they may, and often do, operate to postpone or completely prevent that "physiologic splinting" of the human unit which, of itself, may go a long way toward arresting the disease. This stricture has application also to the use of gold salts, notwithstanding the proven value of it to certain selected cases. It is indeed possible that this and many comparable agencies, alleged to be of value, often fail because of the unbalanced and improperly responsive condition of the host, not yet brought into optimal "alignment."

The syndrome of arthritis constitutes one of the best examples of so-called "psychosomatic medicine." The extent to which this background underlies the whole field of the arthritides is yet to be determined. In the light of recent developments, it is probable that undue emphasis has been placed upon separation of the so-called arthroses from the so-called true arthritides, since both apparently stem, in part at least, from the same stimuli and are largely amenable to the same therapy.

Given a situation in which the neuro-endocrine factors are avowedly many, and subject to varying emphasis, together with an equal number of precipitating or contributory factors, such as age, sex, anemia, infection, etc., one would expect the end picture to be varied. Indeed, Selye[20] concludes, from animal experimentation, "It appears quite possible that, depending upon the acuteness or chronicity of the condition or other incidental factors, the same etiologic agent may manifest itself in different ways and give rise to different types of arthritis."

Summary. 1. Increasing clinical experience and animal experimentation suggest that the ultimate nature of the rheumatic or arthritic process, at least so far as atrophic arthritis and hypertrophic arthritis are concerned, depends in part upon imbalance within the neuro-endocrine system.

2. This imbalance doubtless involves several links of the system rather than a single outstanding dislocation.

3. Clinical evidence suggests, as in most pathologic processes, that the early steps in such dislocations often permit of complete restitution by means of what may be called "physiologic splinting."

4. The basic means necessary to the above ends are relatively simple and center around a programme of conditioned rest and the achievement of an "equilibrium." Such measures should not be divorced, however, from that point of view toward the therapy of arthritis which envisages all departures from normal and considers all relevant and appropriate measures of treatment.

5. Some dislocations of the neuro-endocrine system permit or require "replacement therapy." On the other hand, many cases present no indications or justification for such measures. Some cases are apparently referable in part to overactivity.

6. In certain instances, of overactivity especially, though also in most others, mild sedation, under conditions of complete rest, will aid in restoring equilibrium.

7. With or without the use of "replacement therapy," the plan of

treatment discussed offers the only promise of bringing to bear influences upon the situation so generic as to affect multiple imbalance within the neuro-endocrine system.

8. Countless arthritics are open to great amelioration or arrest of the arthritic process through the application of physiologic principles which often appear too simple and obvious to deserve serious consideration.

9. Many cases of rheumatic disability in the Armed Forces in this country belong in some of the categories considered in this text. They doubtless represent a form of "laboratory experiment" induced by the war in young men not ordinarily exposed in large numbers to sustained pressure. It seems probable that therapy for some of them should include, when necessary, the principle of "physiologic splinting" discussed. Rigidity in carrying out this principle is usually essential.

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POLIOMYELITIS IN PREGNANCY

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and

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During the epidemic of poliomyelitis in the fall of 1943, 6 women with poliomyelitis were admitted to our hospital, 4 of whom were

pregnant. Since the number of such cases in the literature is not great, a report of these cases seemed indicated, especially because of the ratio of the incidence in pregnant and non-pregnant women.

Case Reports. Case 1. Mrs. L. C., aged 26, pregnant 2½ months, entered South View Hospital September 19, 1943, with the complaint of pain in the back and tenderness of the right lumbar area which began August 28, 1943. Temperature on admission was 99.6° F. *Physical examination* revealed hyperesthesia of the right lumbar area, paralysis in the left iliopsoas, and right peroneal and tibialis muscles. There was spasm of the left and right hamstrings, and the patellar and Achilles reflexes were absent.

Laboratory Findings. Spinal fluid, 14 cells per c.mm.; 100% lymphocytes; smear, no bacteria; pellicle test negative for tubercle bacillus; dextrose, 62 mg. per 100 cc.; chlorides, 684 mg.; total protein, 67 mg.; globulin, faintly positive; gold sol, low tabetic curve; Kline and Kahn tests negative; culture, no growth in 48 hours. W.B.C. 8000; hemoglobin, 75%.

Treatment instituted the 1st hospital day and continued for 6 days, consisted of prostigmine, gr. 1/200, at 9 A.M. with hot foments applied to the entire body at 10 A.M. and 2 P.M. The patient was released on the 7th hospital day, with some spasm still present in the hamstring muscles bilaterally, weakness of the quadriceps bilaterally, and weakness of the right gastrocnemius and the extensors of the right foot. There was no complaint of tenderness at this time.

Case 2. Mrs. E. J., aged 25, pregnant 4½ months, entered September 23, 1943, complaining of fever, vomiting and coryza for 2 previous days, and of stiffness of the neck with pains in the back on the day before admission.

Physical examination revealed a hyperirritable, hyperesthetic, stuporous, dehydrated female with severe respiratory distress. Arms and neck were flaccid, although some degree of voluntary control remained. Complete paralysis of the pharyngeal muscles of deglutition and partial paralysis of the intercostals, rectus capitus and right sternocleidomastoid were noted. Pupils were constricted and vertical nystagmus was present.

Laboratory Findings. Spinal fluid, pressure slightly increased; cells, 112 per c.mm.; differential: 98% lymphocytes and 2% neutrophils; dextrose, 67 mg. per 100 cc.; chlorides, 697 mg.; total protein, 44 mg.; Kahn and Kline tests negative; gold sol, low paretic curve; culture, no growth in 24 hours. Similar findings were reported on the following day.

The patient was given prostigmine, gr. 1/100, and atropine, gr. 1/150, on admission, and hot foments were applied to the neck and chest. She became comfortable for a short time, then a rapidly downward course ensued. Continuous oxygen was instituted and prostigmine repeated. Respirations became weaker, pulse rapid, and temperature elevated. Signs of consolidation were elicited in the left lung. The patient died on the 2nd hospital day. Cause of death was given as bulbar poliomyelitis with complicating terminal pneumonia.

Case 3. Mrs. L. W., aged 21, pregnant 7 months, entered September 1, 1943. She had become ill on August 25, 1943, with headache, vomiting and fever. Headache persisted and on August 26 she complained of aching all over. On August 29, she experienced numbness and weakness in her arms with a similar condition developing in her legs 2 days later.

Physical examination revealed generalized tenderness with questionable hyperesthesia, spasm in the neck muscles, and a positive right Kernig's sign. Paralysis was present in both left and right wrists, especially on extension, in both elbows on extension and flexion, in both shoulders on elevation, and in both hips on flexion and abduction. Abdominal reflexes and the left patellar reflex were absent, but the Achilles reflexes were present. Abdominally a tumor of pregnancy of approximately 5½ to 6 months size was palpated. Fetal heart tones were heard slightly to the right of the midline. The presenting part was not palpated on rectal examination.

Laboratory Findings. W.B.C. 7200; R.B.C. 4.4 million. Spinal fluid: cells, 151 per c.mm.; 100% lymphocytes; sugar, 67 mg. per 100 cc.; chlorides, 677

mg.; globulin, faintly positive; gold sol, 1,122,100,000; and culture, no growth in 24 hours.

The patient was transferred to the Wisconsin General Hospital at Madison on September 14, at which time all but the plantar and wrist reflexes were absent, and a total quadriplegic paralysis was present except for slight flexion of the fingers of the right hand. There she received daily Kenny treatment and her gestation was closely followed. On October 16, 1943, because of a slowly rising blood pressure, labor was medically induced and a 5 pound 13½ ounce baby was delivered by breech extraction, completely normal except for a slight asphyxia possibly due to some prolapse of the cord.

CASE 4. Mrs. L. P., aged 32, was transferred to South View Hospital on September 9, 1943, from Milwaukee Hospital, where 3 days previously, she had delivered a full-term normal infant. She had become ill 7 days prior to admission with complaints of backache and pain in the left leg. The following day stiffness of the neck developed with increasing backache and leg pain, and upon admission she complained of pain in both lower extremities.

Physical examination revealed an apprehensive female with neck rigidity, spasm in the back muscle groups and sacrospinalis muscles bilaterally. Gross paralysis of the left leg and paresis of the right leg were present. Kernig's sign was elicited. The left patellar reflex was absent.

Laboratory Findings. Spinal fluid, clear; pressure normal, cells, 100 per c.mm.; dextrose, 47 mg. per 100 cc.; chlorides, 695 mg.; total proteins, 120 mg.; gold sol, negative; Kahn and Kline tests, negative.

Upon admission, routine postpartum care was immediately started. On the 2nd hospital day treatment was begun with prostigmine, gr. 1/200, and atropine, gr. 1/150, at 9 A.M. and application of hot foments to the lower extremities, body and neck at 10 A.M. and 2 P.M. This treatment was routine during the 17 days of hospitalization and she had no complaints referable to the therapy. The pain in the legs and the spasm of the back and neck muscles disappeared, while some spasm of the hamstring muscles remained.

Discussion. Poliomyelitis occurs infrequently in pregnancy. In his review in 1941, Aycock[1] found 28 reported cases of pregnancy complicated by poliomyelitis, and contributed another 28 cases from his personal records. A more recent review of the literature by Weaver and Steiner[8] lists 75 cases to which may be added the 2 of Harmon and Hoyne,[6] 3 described by Hürny[7] and 1 by Biermann and Piszczek.[3] These, with our cases, bring the total reported to 85.

In an experimental study of pregnancy and poliomyelitis, Weaver and Steiner[8] report that 3 of 13 cotton rats, inoculated during the first trimester of pregnancy, resisted infection with poliomyelitis virus. All animals inoculated in the second and third trimester as well as all virgin animals were uniformly susceptible. Furthermore, the incidence of poliomyelitis in the 75 human cases cited by these authors when divided into trimesters is as follows: first trimester, 17.1%; second trimester, 34.3%; and third trimester, 48.6%. Weaver and Steiner feel, then, that their results indicate a significant increase in resistance to poliomyelitis in early pregnancy over the later months of pregnancy and over the non-pregnant state.

The following analysis of the clinical data would not seem to support the latter conclusion. Brahdy and Lenarsky,[4] using the data from the 1931 epidemic, reported 1010 cases of poliomyelitis at the Willard Parker Hospital, 30 of which were over the age of 19. Of the 30 cases, 15 were women and 3 of them were pregnant (20%). Aycock[1] included a personal communication from Vaughan regarding 528 polio-

myelitis cases in Detroit (1939), 255 of whom were paralytic. Eleven of the female paralyzed cases were over the age of 21, and 3 of these women developed the disease during pregnancy (27.3%). In our 1943 series, there were 41 cases of poliomyelitis at the Milwaukee Isolation Hospital, 9 of which were over 19 years of age. Of these 9 cases, 6 were females, 4 of whom were pregnant (66.7%). These experiences suggest, then, that pregnancy may increase rather than decrease a woman's susceptibility to poliomyelitis.

Before discussing further the relation of pregnancy to susceptibility to poliomyelitis, it might be well to comment on the studies of Draper.[5] He was the first to attempt a correlation between morphologic characteristics and incidence of the disease, describing a "poliomyelitic type." After anthropometric studies of the face, jaws, teeth, interpupillary space, hand index, biliac-biacromial diameter ratio, etc., he concluded that persons susceptible to the virus of poliomyelitis are of a special constitutional type which differs from that of non-susceptible individuals.

Aycock[2] regarded the correlation between the poliomyelitis type of Draper and the findings of his anthropometric studies as indicative of an imbalanced or inefficient endocrine system. He studied this problem by castrating a group of female monkeys and injecting them, along with normal controls, with poliomyelitis virus. Some of the castrated monkeys were first prepared by receiving a course of estrogen therapy. There was a significant difference in susceptibility to poliomyelitis in the non-estrogen prepared monkeys as compared with the estrogen prepared animals, the latter group proving more resistant. He further concluded that the injection of estrogenic material into castrated female monkeys enhanced their resistance to the virus and delayed the onset of the disease in those who were destined for infection. Other experiments, in which comparative urinary estrogen assays were done on chronic poliomyelitic patients and control individuals, revealed a higher average estrogen content in the urine of poliomyelitis patients. Although he mentions the possibility that this finding might be a sequela rather than a contributing factor, he was inclined to think, in view of epidemiologic considerations, that the outpouring of the estrogens is a reflection of a physiologic condition which had been present before the onset of the disease. Such a physiologic character of the increased susceptibility to poliomyelitis is further borne out by its seasonal occurrence, climatic variations, and constitutional specificity.

Both the work of Draper and that of Aycock, therefore, support the theory that the endocrines can influence resistance or the susceptibility to anterior poliomyelitis. With pregnancy, ovarian function is increased with resulting rise in estrogen and progesterone levels together with the appearance of a hormone, gonadotropin. Thus one might wonder whether the changed concentration of estrogens in pregnancy might increase the susceptibility of the gravid woman to the disease.

It is possible, too, that other changes than those in the gonads are

concerned, *i. e.*, in the pituitary or in the whole endocrine system, since all the glands of internal secretion are so closely interrelated. One might even speculate as to the effect of fetal endocrine secretion on the mother. The possible rôle of the thymus, if we may call it a gland, is particularly intriguing. It develops rapidly in the fetus, and in postnatal life its period of greatest development closely parallels maximum susceptibility to poliomyelitis.

Whatever the true mechanism of resistance to poliomyelitis may be, this concept of a relation between altered endocrine function in pregnancy and increased susceptibility, is an interesting approach to the problem generally and seems to us to merit further study. Suggested avenues of investigation are: (1) the occurrence of the symptoms and signs of the disease in relation to the menstrual cycle; (2) the effect of estrogens on the course of the acute disease in humans (both pregnant and non-pregnant); (3) an assay of urinary estrogens in the acute poliomyelitic pregnant and non-pregnant female; (4) studies of the thymus gland in poliomyelitic women, both pregnant and non-pregnant, by Roentgen ray and postmortem examination; (5) comparison of thymic tissue and thymic extract in pregnant and non-pregnant women; (6) effect of fetal monkey thymic extract on the susceptibility of thymectomized female monkeys subjected to the virus of poliomyelitis; (7) effect of fetal thymus extract on estrogenic production by assay of urinary estrogens.

There was no evidence of poliomyelitis in the 2 living babies born of 2 of the poliomyelitis cases described, nor was the fetus of the 1 mother dying of the disease affected. These observations agree with those of most other workers who find that poliomyelitis is not transmitted from the mother to the fetus *in utero*.[2,3,4,5,6]

Summary. 1. Case histories are presented of 4 pregnant women who developed anterior poliomyelitis.

2. The high incidence of pregnant women among adult females contracting the disease leads to the conclusion that pregnancy increases susceptibility to poliomyelitis. In our series, 4 out of 6 poliomyelitic women were pregnant; Aycock mentioned 3 out of 11 cases; and Brahdy and Lenarsky presented 3 pregnancies in 15 cases, making a total of 10 pregnant women among 32 adult females. Thus 31.3% of these poliomyelitis cases were pregnant. It is thought that this figure is minimal, since the result is based on the incidence of pregnancy and poliomyelitis in all female adult poliomyelitics, including those not married.

3. Evidence has been summarized which suggests that the increased susceptibility to the disease in pregnancy may possibly be due to the change in ovarian secretion at that time, although pituitary dysfunction and fetal hormones upsetting the mother's balance may also be suspected.

4. In the 4 cases of poliomyelitis complicating pregnancy at the Milwaukee Isolation Hospital, delivery of 2 normal children, and examination of 1 fetus in a dead mother, confirmed the opinion that

poliomyelitis in the mother has not affected the newborn child, nor does it hamper normal spontaneous delivery.

5. Possible studies on the endocrinologic approach to poliomyelitis are suggested.

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PROGRESS
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PATHOLOGY AND BACTERIOLOGY

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THE RELATION OF STREPTOCOCCI TO HUMAN DISEASE: IMPORTANCE OF IDENTIFICATION AND NOMENCLATURE

II. STREPTOCOCCI OTHER THAN THOSE OF GROUP A

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ALTHOUGH the more acute and severe streptococcal infections of man are usually due to the beta hemolytic streptococci of Lancefield's serologic Group A, as related in Part I of this review,[7] it is now recognized that there are many sporadic cases of infection by those of Groups B, C, D, F and G. Cultural differences among the streptococci of these groups began to be recognized before they were differentiated serologically and helped to explain many anomalous clinical results, difficult to understand when all of these streptococci were reported as *Streptococcus hemolyticus*. Nevertheless, serologic grouping by the precipitin method of Lancefield[17] or its technical modifications[5] not only saves time but also indicates antigenic relationships between different species of streptococci. It appears that all members of a species of streptococcus belong to a single serologic "group" but that more than one species, as determined by cultural study, may exist within each group. The groups may also be subdivided into a number of serologic "types" by precipitation or agglutination. The types do not always coincide with species and there may be a number of different types within a single species. The determination of type is very useful for tracing sources of infection or mode of contagion. For better understanding of the pathology, epidemiology and therapy of streptococcus infections it is desirable that the serologic group, the species and the serologic type of each strain shall be determined.

The beta hemolytic streptococci of serologic Group B usually produce double zones of hemolysis about deep colonies in blood agar plates when cultivated and observed under favorable conditions (Brown, 1937[4]). Since the initial zone of hemolysis is usually small with poorly defined

periphery, it may be mistaken for the alpha prime appearance, as was done by Hansen, Hucker and Snyder,[15] unless it is studied in optical section under the 16 mm. objective of the microscope.* The Group B hemolytic streptococci characteristically hydrolyze sodium hippurate and ferment trehalose but not sorbitol. They may be subdivided according to source and fermentation of lactose and salicin (Table 2).

TABLE 2.—GROUP B HEMOLYTIC STREPTOCOCCI DIVIDED ACCORDING TO SOURCE AND FERMENTATION OF LACTOSE AND SALICIN

Species	Source	Fermentation of Lact.	Fermentation of Sal.	Prevalence† at Johns Hopkins Hospital
I. *S. opportunus* Brown 1939	Human	−	+	26 strains
II. Not named	Human	+	+	22 "
III. *S. mastitidis* Guillebeau 1890 (*em.* Frost and Engelbrecht 1940)	Bovine	+	+	
IV. *S. asalignus* Frost, Gumm and Thomas 1927	Bovine	+	−	1 strain

Apparently these closely related species are entities and it is convenient to refer to them by names. *Streptococcus opportunus* is found frequently in the normal human throat and vagina. It may assume the rôle of an opportunist pathogen, producing infections in various parts of the body and rarely fatal septicemia. Usually the source of such infections may be traced to the throat or genito-urinary tract of the patient. Group B hemolytic streptococci fermenting both lactose and salicin may also be found in the human throat and vagina and have the same pathogenic significance as does *S. opportunus*. The lactose +, salicin + strains from human sources are culturally similar to *S. mastitidis* which is one of the most common causes of bovine mastitis but there is some evidence that they are not identical. Brown,[6] confirmed by Simmons and Keogh,[21] found the human strains more pathogenic for mice than were the bovine strains. The latter authors also found the human and bovine strains to belong to different serologic types within Group B. This appears the more significant since the human strains were from persons not associated with the cows or milk from which the bovine strains were obtained. *S. asalignus* also is a common cause of mastitis and has been found by Frost and Engelbrecht[14] in the throats of milkers, and by Plummer[19] in the throats of children consuming infected milk. It has not been reported from the human genito-urinary tract. At one autopsy we isolated it from the heart blood, lung and spinal fluid of a child who died of lead poisoning and whose lungs showed evidence of aspiration of food or vomitus. Frost and Engelbrecht also report the frequent presence of *S. mastitidis* in the throats of milkers. It is obvious that such persons may act as transient carriers of *S. mastitidis* and *S. asalignus* without suffering ill-effects and that the former organism is indistinguishable culturally from the lactose +, salicin +, Group B hemolytic streptococcus found in the throats, genito-urinary tracts and occasional lesions of persons not exposed to mastitis milk. While there is no evidence that the bovine strains are pathogenic for man, Little[18] has shown that mastitis may be produced by the injection of human strains into the bovine udder. As is the case with *S. pyogenes*, it may be that occasionally a cow is accidentally infected by a careless

* For the recognition of alpha and beta zones microscopic study of deep colonies is essential. The study of surface colonies only is unsatisfactory.[13]

† Strains from 2349 autopsies from which culture material was taken during a 6-year period.

milker. There is no evidence that Group B streptococci are of epidemic significance. Of 1070 strains of streptococci from urine specimens of patients in the gynecologic and obstetrical services of Johns Hopkins Hospital, 6% were Group B beta hemolytic streptococci. Of 232 strains of streptococci from the uteri of patients with febrile puerpera, only 3 were Group B strains.

Similar to *S. mastitidis*, except that it produces alpha zones in blood agar, is *S. agalactiæ* Lehmann and Neumann 1896 (*em.* Frost and Engelbrecht 1940). It belongs to serologic Group B and is a common cause of bovine mastitis. It has not been found in human disease nor reported from the human throat although there is no apparent reason why it should not occur there as a transient.

Beta hemolytic streptococci of serologic Group C may produce disease in man and other animals. Some may be harbored by the normal human throat and vagina. The known species are listed in Table 3.

*S. zoöepidemicus** is appropriately described as "the animal pyogenes"; among animals it plays a rôle similar to that of *S. pyogenes* among men. Although it has been found in the throats of persons in close association with animals[14] it is doubtful whether it is pathogenic for man. Until the differential value of trehalose and sorbitol was recognized and serologic grouping was employed it could not be distinguished from *S. pyogenes*.[8,9,10]

S. equi has long been known as the cause of "strangles," a cervical adenitis of horses. There is no reason to believe that it is pathogenic for man.

S. equisimilis has been found in infections of various animals (man, cow, horse, monkey, chicken) and in the normal human throat and vagina. Evans[11] summarizes evidence of the transmission of the infection from horses to man. Because of similar bacteriophage sensitivity she regards those strains which fail to ferment salicin or ferment lactose (IV and V in Table 3) as subgroups of *S. equisimilis*. Human infection by Group C hemolytic streptococci may be local or systemic, mild or severe, sometimes fatal. About 200 strains reported in the literature came from such sources as puerperal sepsis, erysipelas, scarlet fever, hemorrhagic smallpox, mastoiditis, sinusitis, otitis, urinary tract infections, pneumonia, septicemia, abscesses and ulcers in various parts of the body. As compared with Group A streptococcus infections there have been relatively few cases of sore throat and no outbreak of epidemic proportions.

S. dysgalactiæ Diernhofer 1932 (*em.* Little 1939), a cause of bovine mastitis, produces alpha zones in blood agar and is a member of serologic Group C. It has not been reported from human sources.

The streptococci of serologic Group D are collectively known as enterococci (Sherman, 1937[20]). Their normal habitat is the intestine of man and many other animals. Like many other bacteria in the intestine they may cause disease by extension or conveyance from the intestine to susceptible tissues or organs. They are not highly virulent but are more resistant to heat, disinfectants and drugs than are other streptococci. In stained smears they often appear as slightly elongated or oval Gram-positive cocci in pairs rather than in chains, and, in stained sections of tissue, may be mistaken for pneumococci. The known species encountered in human infections are listed in Table 4.

The enterococci account for nearly 50% of the streptococci isolated from autopsy material (Table 5); the beta hemolytic species, about 7%, and the alpha species, about 40%. About three-quarters of them were from heart

* The name appears to be valid although one might wish that it had been *epizoöticus*.

TABLE 3.—BETA HEMOLYTIC STREPTOCOCCI OF SEROLOGIC GROUP C

Species	Lact.	Sal.	Mann.	Treh.	Sorb.	Fib.*	Prevalence† at Johns Hopkins Hospital
I. *S. zoöepidemicus* Frost and Engelbrecht 1935	+	+	−	−	+	−	
II. *S. equi* Sand and Jensen 1888 (*em.* Evans 1936)	−	+	−	−	−	−	
III. *S. equisimilis* Frost and Engelbrecht 1940	−	+	−	+	−	(+)	4 strains
IV. } IV and V are regarded by Evans[11] as subdivisions of *S. equisimilis*	−	−	−	+	−	..	3 "
V. }	+	+	−	+	−	..	2 "
VI. Others	−	+	±	±	±	..	3 "

* Lysis of human fibrin.
† See note under Table 2.
(+) Strains from human sources positive.
± Positive or negative.

TABLE 4.—STREPTOCOCCI OF SEROLOGIC GROUP D

Species	Bld. ag.	Prot.*	Lact.	Sal.	Mann.	Treh.	Sorb.	Prevalence† at Johns Hopkins Hospital
I. *S. zymogenes* MacCallum and Hastings 1899 (*em.* Sherman 1937)	Beta	+	+	+	+	+	+	6 strains
II. *S. durans* (syn. *hemothermophilus* Sherman and Wing 1935, 1937)	Beta	−	+	(+)	(−)	(+)	−	1 strain
III. Not named (possibly a variant of *S. zymogenes*)	Beta	−	+	+	+	+	+	46 strains
IV. *S. liquefaciens* Sternberg 1893 (*em.* Orla-Jensen 1919)	Alpha	+	+	+	+	+	+	15 "
V. *S. fecalis* Andrewes and Horder 1906	Gamma to alpha	−	+	+	+	+	+	318 "

* Liquefying gelatin and coagulated serum.
† See note under Table 2.
(+) or (−) Usually + or − according to Sherman, 1937.

blood, lungs and peritoneum, named in the order of occurrence. Doubtless many of these isolations were due to postmortem invasion but there were also cases of enterococcus endocarditis, bacteremia, peritonitis, and mixed culture pneumonia as well as many local infections. Infection of the urinary tract is frequent. Of 1070 strains of streptococci from urine specimens of patients on the gynecologic and obstetrical services of the hospital, about 58% were enterococci, whereas of 232 strains from uteri of patients with febrile puerpera, only 9% were enterococci, none of which was hemolytic. Of 53 beta hemolytic enterococci from autopsy material, 6 were *S. zymogenes*, 1 *S. durans*, and 46 a streptococcus resembling *S. zymogenes* except that it failed to liquefy gelatin or coagulated serum (Species III, Table 4).

TABLE 5.—RELATIVE PREVALENCE OF VARIOUS STREPTOCOCCI

	Urine cultures from gynecology and obstetrics	Uterine cultures from febrile puerperæ	Autopsy cultures
Aerobic	**98.4%**	**24.5%**	**98.0%**
Beta	*12.4*	*2.6*	*31.4*
Group A	0.4	0.9	14.5
Group B	6.0	1.3	6.2
Group C	1.3	0.4	1.5
Group D	3.7	..	7.3
Other than A, B, C or D	1.0	..	1.9
Alpha	*83.2*	*19.3*	*66.0*
Enterococci, Group D	54.0	9.0	40.0
Other alpha strep.	29.2	10.3	26.0
Gamma	*2.8*	*2.6*	
Anaerobic	**1.6**	**69.0**	**1.5**
Beta	*0.1*	*22.4*	*1.5*
Alpha	*0.2*	*10.1*	
Gamma	*1.3*	*36.5*	*Few*
Micro-aerophilic	..	**6.5**	**0.4**
Beta	..	*3.0*	*0.4*
Alpha	..	*1.7*	
Gamma	..	*1.8*	

The streptococci of serologic Group E are not known to be pathogenic for man. The known strains have been from cows' udders showing little or no evidence of mastitis.

During a period of 6 years we have obtained from autopsy material 3 strains of Group F (2 from lungs and 1 from peritoneum) and 4 strains of Group G (3 from lungs and 1 from heart blood) beta hemolytic streptococci. Among the latter none was *S. anginosus*. Two other strains resembled those of Group G culturally and did not belong to Groups A, B, C or D but no G serum was available at the time. Obviously there are not enough strains of Groups F and G to warrant any other conclusion than that they have been found rarely in our autopsy material.

Although the alpha enterococci belong to serologic Group D and certain alpha mastitis streptococci belong to Groups B and C, most of the so-called "viridans" streptococci of human origin do not belong to any of Lancefield's serologic groups. These occupy a very prominent place in throat cultures, are found in all normal throats, and so it is difficult to ascribe any significance to them when found there. They are opportunist pathogens and our appraisal of them must be derived from their presence in pathologic lesions, the blood stream, the urine, or the uterus when there is clinical evidence of infection. The species commonly encountered are listed in Table 6.

TABLE 6.—VIRIDANS STREPTOCOCCI

Species	Lact.	Sal.	Mann.	Milk*	Prevalence† at Johns Hopkins Hospital
I. *S. mitis* Andrewes and Horder 1906 (*em.* Holman 1916)	+	+	−	−	97 strains
II. *S. salivarius* Andrewes and Horder 1906	+	−	−	+	41 "
III. *S. ignavus* Holman 1916	−	−	−	−	39 "
IV. *S. equinus* Andrewes and Horder 1906	−	+	−	−	22 "

* Coagulation of milk. † See note under Table 2.

It is not to be assumed that lactose, salicin, mannitol and milk are the only test substances required to diagnose these species. They have the other differential characteristics of the "viridans division" listed in Sherman's Table 1.[20] In Sherman's Table 3 *S. mitis* is included with *S. salivarius* and *S. ignavus* with *S. equinus* by indicating salicin fermentation as ±. We do not find ± signs of much differential value and, since we have no evidence that the salicin fermentation is variable, prefer to give different names to these streptococci. We have found *S. mitis* about twice as frequently as *S. salivarius*, and *S. ignavus* more frequently than *S. equinus* (Table 6). We notice no difference in the distribution or localization of these species in autopsy material; most of the strains are from lungs and heart blood. Endocarditis may be caused by any of them or by enterococci. These 4 species of viridans streptococci comprise about 26% of streptococci from autopsy material, 29% from urine specimens and 10% from uteri (Table 5).

Reasons similar to those which we urged against the use of the name *S. hemolyticus*[7] influence us to disapprove of the name *S. viridans*. These names are too broad to be used in a specific sense. There are too many hemolytic streptococci and too many viridans (green-producing) streptococci for inclusion in single species. We shall learn more about drug therapy when we cease to read reports of *S. viridans* endocarditis treated successfully (or unsuccessfully) with so-and-so.

The streptococci which produce the gamma appearance in blood agar (neither hemolysis nor greenish discoloration about deep colonies[3]) are negligible in our autopsy series and comprise less than 3% of the streptococci from urines and uteri. This may be due to several causes. Differences in the basic agar and the species of blood used are factors. In some laboratories it is not customary to incubate blood agar plates for 48 hours and then reëxamine them after refrigeration overnight; some alpha zones are not apparent until after refrigeration. This is notably true of some strains of *S. fecalis* and has led Topley and Wilson[22] to describe their appearance as gamma rather than alpha; actually in 24 hours the deep colonies of *S. fecalis* are likely to appear as gamma and later as alpha.

The anaerobic and micro-aerophilic streptococci remain to be discussed. The largest incidence of anaerobic streptococci is to be found in uterine cultures (69%) (see also Harris and Brown[16]). It appears that all streptococci grow well anaerobically. This has led some workers to incubate all primary cultures anaerobically and is not bad practice provided later attempts are made to cultivate the isolated streptococci aerobically. Some streptococci which require anaerobic conditions for isolation soon acquire the ability to grow aerobically and so are not true anaerobes. Under anaerobic conditions the alpha appearance may be suppressed, resulting in either the beta or gamma appearance.[3] It may be for this reason that the incidence of anaerobic alpha strains among our uterine cultures is relatively small (10%). In this laboratory Brewer's thiogly-

collate medium[2] has been found excellent as an enrichment medium for all streptococci.[12] When pathologic material is inoculated into this medium both anaerobic and aerobic streptococci are isolated more frequently than by primary plating in blood agar although the latter is also advisable in order to obtain relative counts of the number of bacteria present in the original material. In our autopsy and urine series of cultures the anaerobic and micro-aerophilic strains comprise less than 2% of the streptococci and we can attach no special significance to them.

Since the year 1938 the sulfonamides have been used extensively for the treatment of streptococcus infections at the Johns Hopkins Hospital. In the same year we started grouping all beta hemolytic streptococci isolated from autopsy material. In the culture records for the years 1932 to 1938 we are able to recognize almost all of the strains of Groups A, B, D, those of Group C which we described as "equi-like" (now called *S. equisimilis*), and a few others which probably did not belong to any of the above groups. In Table 7 is an enumeration of the strains isolated during these two 6-year periods from autopsy material.

TABLE 7.—STRAINS OF BETA HEMOLYTIC STREPTOCOCCI ISOLATED FROM AUTOPSY MATERIAL

	Group A	B	C	D	Others
1932–1938	190	42	29	40	12
1938–1944	112	49	12	55	18

There appears a marked decrease in the number of strains of Group A, most of them *S. pyogenes*. If the numbers are significant there is also a decrease from 29 to 12 in the incidence of Group C streptococci but it is possible that some of those listed for 1932–1938 may have been of Groups F, G or H. The incidence of streptococci of Groups B and D shows no significant change. It may be that these figures support what we find to be the opinion of clinicians; that sulfonamide therapy is of greatest value in the treatment of Group A streptococcus infections, of no value for Group D infections, and of questionable value for infections by streptococci of other groups. These opinions are supported by the experimental results of Bliss, Long and Feinstone.[1] There is an impression that the sulfonamides are of some value in the treatment of urinary tract infections by Group B streptococci. Our data do not permit any opinion as to the value of sulfonamides in infections by other than the beta hemolytic streptococci. Only by a correlation of more exact systematic bacteriology with clinical observation can this information be obtained.

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XUM

PREVENTIVE MEDICINE AND EPIDEMIOLOGY

UNDER THE CHARGE OF
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SEASONAL PREVALENCE AS A PRINCIPLE IN EPIDEMIOLOGY

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Bacteriologic methods for the detection of infectious agents in the determination of infectious periods of disease, the establishment of subclinical infection, healthy carriers or other sources of infection, and immunity tests for surveying previous infection are now in common use in epidemiology. Knowledge of the epidemiology of many infectious diseases has been gained very largely, if not entirely, from the use of these precise methods. In some diseases, laboratory procedures of this kind have served more to verify or clearly define concepts already arrived at by the older method of deduction and inference from observation of the distributional features of disease. In others, their use has been responsible for the amendment or rejection of erroneous hypotheses which had been based on studies of the distribution of the disease alone. In still others not amenable to such techniques for one reason or another, the older method of inference and analogy must still be relied upon, and, when properly used as a tool in epidemiology, does not necessarily carry a risk of error greater than that which exists in the experimental method. At any rate, it serves to eliminate large numbers of unlikely hypotheses and to aim experimental approaches toward a limited number amongst which the right one is to be found. There are many examples of the successful use of the inferential method: Budd's conception of typhoid fever—including chronic carriage, the presence of the infecting agent in intestinal discharges and its transmission through contaminated water supplies—developed from his observations of the distribution of the disease in rural areas long before the discovery of the typhoid bacillus, was later to be abundantly confirmed by the newer methods. But the great development of the experimental method has thrown the older method into the shadow. As Theobald Smith[34] said, "The latter looks at things in nature, describes and compares them, and deduces from such comparisons certain underlying concepts. The experimental method takes the same phenomenon and tries to check or limit all but one of the activities entering into it so that this one activity can be observed, recorded, measured, and weighed. .... Both methods have their special advantages and disadvantages." When we witness some of the broad epidemiologic generalizations drawn from isolated experimental findings we cannot but be reminded of Theo-

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bald Smith's further statements that "the experimental method must not let too many machines get between it and the whole and must find some way of putting the fragment surgically removed for experimental purposes back into the whole" and that "the comparative method is frequently in position to restrain the generalizations deduced from experimental procedures and to keep the experimenter from steering away from the goal, which is an understanding of the totality."

The mode of spread of the infectious agent has been the central idea in epidemiology. Inferences, both from experimental findings and from various distributional features of disease, have tended to be directed toward mode of spread—the actual mechanics of transfer of the microbial agent from one to another. Good reason for this emphasis on mode of spread lies in the fact that in many diseases it not only is the important determinant, but also offers a point of attack in practical control. But that it has been stressed at the expense of consideration of other factors which act as major determinants is well expressed in the writings of an earlier period before microbiology had gained the ascendency. In 1750 John Huxham[15] wrote, "The highly putrid, malignant Fevers many Times arise from mere antecedent Acrimony of the blood . . . . yet generally the pestilential and petechial have their Origin from Contagion; and may therefore affect Persons of all Constitutions, which will of Course produce a great Diversity of Symptoms . . . . For, as the received Contagion acts nearly in the same Manner as Acrimony, it will have very different Effects, when it invades a strong vigorous Constitution . . . . from what it will, when it attacks a weak, lax Habit . . . ." And when he speaks "Of the Power of the Winds and Seasons in producing these Distempers" and describes their effects on the body (fluids and solids) together with what might be called his experimental observation that "It is Fact, that *cæteris paribus*, Blood drawn, in such prevailing Constitutions of the Atmosphere, is constantly found more dense and viscid than in long moist warm Seasons," he evidently was no less sure of his epidemiologic inferences—seasonal variation in constitution—than we are today when we attribute seasonal variation in infectious disease exclusively to seasonal variation in mode of spread.

Seasonal fluctuation is not only a very general epidemiologic principle, but for a given disease is one of its most constant epidemiologic characteristics. Most infectious diseases exhibit marked variations with season and these are remarkably constant from year to year. The influence of season is most strikingly evident in the variation in seasonal curves at different latitudes amounting to a complete reversal of months of prevalence in corresponding latitudes in the northern and southern hemispheres.

The constancy of seasonal prevalence of disease has made it a favorite basis for epidemiologic inference. In a number of diseases it is clear that seasonal variation is determined by corresponding changes in the opportunities for transmission of the infectious agent (as influenced by the bionomics of the vector). This unmistakable association between mode of spread and season in certain diseases has been generalized into a law of seasonal prevalence which has, in turn, led to the grouping of diseases with reference to modes of spread on the basis of their seasonal prevalence alone. As Madsen[21] has pointed out, "Des l'antiquité, on s'est rendu compte que les maladies présentaient une intensité variable selon les saisons. Hippocrate distinguait déjà entre les maladies hivernales et printanières, d'une part et les maladies estivales et automnales d'autre part." One of the most sweeping applications of this "law" of seasonal

prevalence is the doctrine to the effect that infections transmitted through the upper respiratory tract are all winter diseases because of a hypothesized increased transmission resulting from the "closer crowding" of winter; and the converse that a disease not exhibiting a similar seasonal prevalence must have a different mode of spread. This has been emphasized in a very recent paper by Wells[41] in the statements that: "The concentration of microörganisms in the air is an equilibrium between the rate of addition and rate of elimination, the latter being determined primarily by ventilation . . . . In those localities where there is a marked difference between summer and winter temperatures, incidence of infection (and of the disease where the two are synonymous, as in the case of measles and chickenpox) will likewise show a marked sensitivity to seasonal change. . . . ." And finally, "Seasonal patterns will vary with climate, since this affects the length of the season when ventilation is impeded by closed windows." However, the seasonal curves of upper respiratory disease in northern and southern latitudes do not always bear out these assertions without the assumption of differences in such factors as rate of accumulation of susceptibles.

Insect-borne diseases for the most part come under a generalization of summer prevalence, but even here there is a striking exception—typhus fever. If one argued the mode of spread of typhus fever on the basis of seasonal prevalence alone, according to the doctrine so rigidly adhered to in diseases grouped as upper respiratory (forgetting all established facts concerning the louse and its habits), an inference that typhus is insect-borne would hardly be made. Such a situation, now highly imaginary of course, actually existed in 1814 when Hildenbrand wrote, "The source of all typhus matter is to be looked for solely in concentrated human effluvia." This was still quoted by Hirsch[13] in 1883 who added the idea that "overcrowding in filthy and unventilated rooms affords the essential condition for the development of typhus-foci, and for the spread of the disease. . . . . The diffusion of the disease, or the conveyance of the morbid poison, takes place equally by the air surrounding the patient, as by personal intercourse and by objects—healthy men or things—which become carriers of the poison that clings to them."

The essential point in the present connection is that no one would now question the insect transmission of epidemic typhus because it is not a disease of summer prevalence as are most of the insect-borne diseases. But the establishment of the exception to the rule in the case of typhus, a member of the group of diseases in which the mechanism of seasonal fluctuation is better understood, seemingly has not yet opened in the minds of many the possibility of exceptions in the infections transmitted directly from man to man. In this group where, after all, the exact mechanism which determines seasonal prevalence is still conjectural, there is still insistence that all members of the group should conform to the majority pattern of seasonal prevalence. In both insect-borne and contact disease groups, epidemiologic activity represents the interplay of parasite, environment and host. The discrepancy in understanding of the two groups in respect to mechanics of transmission doubtless lies in part to the fact that in the former, all but one of the activities can be checked or limited so that this one can be observed—particularly true of the environmental factor in disease in which intermediary sources of infection are involved. In the latter group in which transmission is directly from man to man, the activities of parasite, environment and host are so closely inbound that one cannot be "surgically removed" for experimental pur-

poses and then put back into the whole, in the Theobald Smith sense. As Madsen[21] pointed out, "Pour un groupe important de maladies, celles que transmettent les insectes, l'action des saisons semble facilement explicable; il existe un parallélisme entre les fluctuations saisonières de ces maladies et les fluctuations correspondantes de la vie des insectes, entre la periodicité de la peste, du typhus exanthématique, du paludisme, et le rythme vital de la puce, du pou, du moustique." And yet season is no common denominator of disease, for the same disease, having more than one mode of spread, may exhibit different seasonal curves, distinguishing each of its modes of spread. In tularemia, 4 seasonal curves can be distinguished dependent on whether it is transmitted by the ticks *D. andersoni*, *D. variabilis*, the horsefly *Chrysops discalis* or directly from rabbit to man (Chart 1). Even in this group of diseases where seasonal preva-

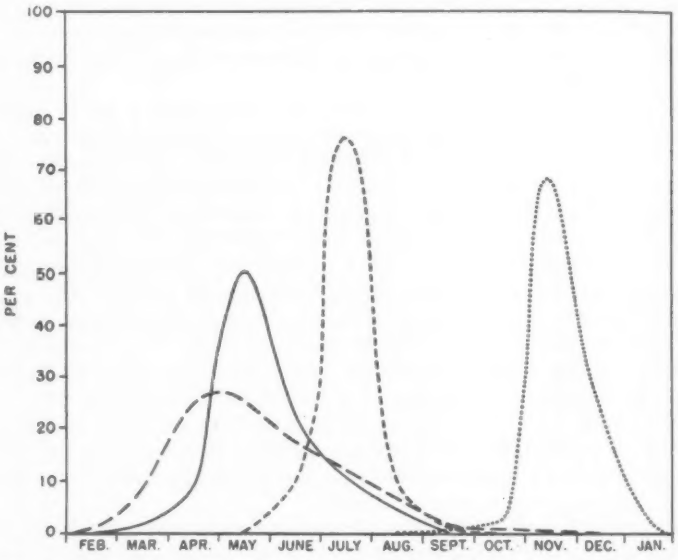

CHART 1.—Seasonal prevalence of tularemia. (Schematic.). Transmitted by: *D. andersoni* ———; *D. variabilis* — — —; *Chrysops discalis* – – – –; rabbit contact ———. (Data from Pub. Health Rep., **52**, 107, 1937.)

lence can be so closely associated with variation in the frequency of transmission, it might be stated, although the point is academic rather than practical, that seasonal prevalence may be due in the strict sense to seasonal variation in the virus reservoir rather than to seasonal variation in the actual mechanism of transfer from the insect to man. Outbreaks of malaria, for example, have occurred in midwinter, where opportunities were provided for the maintenance of mosquito reservoirs in indoor cisterns.

Although as Madsen said, the action of season in the group of insect-borne diseases seems easily explainable, the action of season on the upper respiratory infections, on the other hand, does not seem so easily explainable when the question is carried beyond the simple generalization that this group of diseases—herd or crowd diseases—is influenced by seasonal differences in crowding in summer and winter, which, in turn, affect the

ease with which their infectious agents are transferred from person to person.

Crowding. That the dissemination of infectious agents transmitted directly from man to man is favored by closer aggregation of people need hardly be stated. Both rates and extent of dissemination vary directly with density of population, as shown both by urban and rural differences in incidence and age distribution of disease, in urban-rural differences revealed by carrier studies and by immunity surveys, as, for example, the Schick test in diphtheria or the virus neutralization test in poliomyelitis.[3] The association between population density and dissemination reaches its furthest extreme in remote population groups, not large enough to maintain a continuous sequence of transfer from person to person without exhaustion of susceptibles, and in rare instances of "isolated" individuals. The notable example is the outbreak of measles in the Faroe Islands in 1846 following a 60 year absence of the disease, which was the subject of Panum's classic treatise. In Iceland, measles does not occur continuously as in more intermingling population groups, but occurs in epidemics frequently of great intensity, following its reintroduction from without after varying periods of years of complete freedom from the disease. During the period 1911–1939, measles reappeared in Iceland 5 times following intervals of absence of from 1 to 7 years.[10] The first cases in these outbreaks representing the reintroduction of the disease occurred in February, April, July, August and November, and all reached peaks of prevalence in from 3 to 5 months, coming in June, July and November, and twice in January. Following these major outbreaks and continuous with them were 5 discernible secondary increases in cases which are known to represent the movement of the disease into new areas along the limited lines of communication around the periphery of Iceland. A group of explorers came upon a hermit in an inaccessible part of the Snake River canyon. He told his rather unwelcome visitors that he made only one trip a year to the nearest settlement 40 miles away, but stayed just long enough to weigh out his gold dust and get necessary supplies for he always caught cold when he went there. And then he added, "I'll be sick tomorrow because you've been here."[8]

Thus in differently aggregated population groups, measurable degrees of "crowding" are accompanied by corresponding differences in the dissemination of infectious agents. But it cannot be affirmed, nor is there any measurable indication that in a given population the seasonal variation in disease accompanies any corresponding seasonal variation in "crowding."

Pandemic Influenza. Pandemic influenza, a disease in which "spread" is a dominant characteristic, does not exhibit seasonal variation in the manner of many of the upper respiratory infections. Peaks of prevalence, usually far more precipitous than the seasonal undulation seen in other upper respiratory diseases are reached not regularly at the same season, but at any time of the year. The lack of seasonal influence on "spread" is strikingly shown by the simultaneous appearance of epidemics, as, for example, in 1918 in the northern and southern hemisphere.

Difference in Seasonal Prevalence in Diseases With the Same Mode of Spread. It would be expected that seasonal curves of individual diseases in a group transmitted in the same manner would be secondarily affected by such factors as differences in infectious period and incubation period, as well as by differences in population immunity. However, the effect of these secondary factors would not appear to be sufficient to explain

the wide divergence observed amongst the seasonal curves of common upper respiratory infections in the same area. For example, the difference

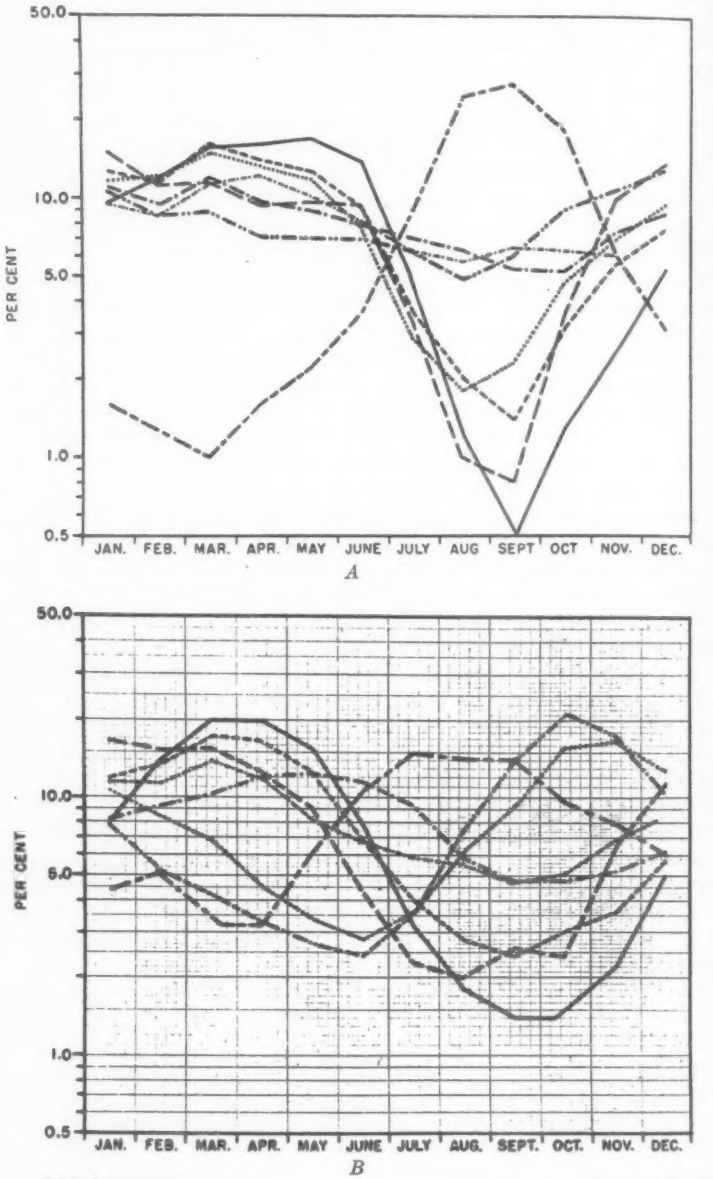

CHART 2.—*A*, Seasonal prevalence in Massachusetts and Connecticut. *B*, Seasonal prevalence in Alabama and Mississippi. (Data from registration states, Pub. Health Rep., 1925–1939.)

in time between the peaks of prevalence of diphtheria and meningitis is actually greater than that between diphtheria and certain diseases classified as "occurring in the opposite season" to that of the upper respiratory infections. If any single seasonal factor, like "crowding" were a major influence in the seasonal prevalence of all of the group of upper respiratory infections, it would be difficult to account for such differences in seasonal curves both in northern and southern latitudes as are shown in Charts 2*a* and 2*b*.

Seasonal Virus Harborage. There now have been established by bacteriologic methods carrier rates which do not vary with season as does the disease which the parasite causes. The prevalence of Type 1 meningococci does not show seasonal differences corresponding to the seasonal variations in the incidence of meningococcus meningitis. The carrier rate for *H. influenzæ* remains more or less constant at a high level throughout the year, suggesting that upper respiratory transmission from person to person occurs as readily at one season as another. Although generally considered to be a saprophyte in the adult, these microörganisms occasionally cause meningitis in children, but as with the meningococcus, disease occurs only in a few of those exposed, at a particular season, and is not necessarily associated with any increase in the carrier rate in the population group in which the cases occurred.

The seasonal increase in hemolytic streptococcus carrier rates has been interpreted as a precursor of an outbreak of streptococcal disease.[32] However, it is not yet clearly established that an increase in the number of carriers is the cause rather than the result of disease in a given population group. Carrier studies are not infrequently initiated in populations in which disease is occurring. Thus a "normal" carrier rate may be given undue weight by the fact that the study is done in the presence of disease occurrence. Furthermore, the seasonal fluctuation in hemolytic streptococcus carrier rates is due to fluctuations in the prevalence of Group A strains, the non-Group A strains remaining at a more or less constant level throughout the year.[31] It seems that if "crowding" *per se* were the explanation for seasonal differences in prevalence, then the non-Group A strains should show similar variation—unless one is willing to apply a hypothesized seasonal difference in "transmission" to a particular group of strains. With reference to seasonal differences in the prevalence of carriers, it should be remembered that seasonal variations in host receptivity to the organism could as well be a factor as seasonal differences in "transmission" as the result of crowding.

Seasonal Variation in Disease Under Uniform Conditions of Infection. Under experimental conditions where the actual transfer of the infectious agent can be held constant, seasonal variation in the resulting disease still occurs, which in certain instances, corresponds closely to seasonal variations in the natural disease.

Südmersen and Glenny[36] observed a seasonal variation in the toxicity of diphtheria toxin for guinea-pigs. Their observations, when expressed in terms of susceptibility, result in a curve remarkably similar to the curve of the seasonal distribution of diphtheria in the northern United States. Pritchett,[28] working with 5 genetically different strains of mice, observed seasonal fluctuations in susceptibility to paratyphoid-enteritidis infection from a low point in the summer months, increasing through the fall and reaching a peak in early spring. Although there were strain differences in degree, the susceptibility of each strain showed similar seasonal variations. Webster[40b] pointed out that the death rates resulting from a spontaneous outbreak of *B. lepisepticum* infection in a rabbit colony showed a seasonal

variation similar to that observed in experimental mouse typhoid. In view of his previous observation[40a] that in an experimental epidemic the virulence of a given strain remained constant, he suggested that the curve of seasonal fluctuation in mortality in the natural epidemic was due to seasonal variations in host resistance rather than to any microbial change concomitant with the occurrence of the epizoötic. Brown and Pearce[4b] have demonstrated a seasonal variation in the susceptibility of rabbits to experimental syphilis, the peak of susceptibility occurring in the late winter and early spring months. Brown, Pearce and Van Allen[5a] reported a similar seasonal fluctuation in susceptibility of rabbits to a transplantable neoplasm. Lillie, Dyer, Armstrong and Pasternack[18] over a period of years, found the intensity of cerebral reaction of mice to St. Louis encephalitis virus, and that of guinea-pigs to endemic typhus rickettsia to be greatest in summer and least in winter. Thus under these experimental conditions where the infectious agent can be held constant in respect to strains, "virulence," dosage and manner of administration, seasonal variations in disease still occur, and these seem clearly ascribable to variations in the test animals. This interpretation finds support in the more basic observation of marked differences in the response of different family lines of experimental animals to the same infection.[19,40c]

Seasonal Variation in Non-infectious Disease. A number of non-infectious diseases are subject to seasonal variation to an extent equal to that of infectious diseases. This fact in itself is enough to show that seasonal variations may result from causes other than mode of spread. Seasonal variation in non-infectious disease may result either from variation in environmental factors or from variation in reaction to the impact of a constant environmental factor, as in pellagra. The seasonal character of pellagra was one of the important bases of the theory advanced early in the study of pellagra that it was an infectious disease. The similarity in the character of seasonal curves of infectious diseases and non-infectious disease suggests that a common factor—like seasonal variation in the host—is involved in both, rather than causes as different as rate of spread and dietary habits.

Seasonal Variation in Physiology. Despite the accumulated evidence that the physiologic range within which the "normal individual" remains "normal" may be subject to wide variation because of extrinsic as well as intrinsic influences, the possibility that the host may vary with season in respect to its reaction to infection has not yet been generally considered as a possible determinant of seasonal distribution of disease. Perhaps the slowness to readily include host variation in epidemiologic concepts has been due to the lack of proper tools for precise studies of the human host with respect to variable reaction to a given infectious agent—such studies not lending themselves readily to the application of bacteriologic techniques usually employed in the study of infectious disease.

There is, however, considerable experimental evidence from other fields on the effect of season on physiology. Seidell and Fenger[33] have shown that there is a seasonal variation in the iodine content of the thyroid gland of sheep, cattle and hogs, and that different seasonal curves are obtained in different latitudes. Martin[24] reported that the iodine content of thyroids collected from sheep in England showed the same variation, although less than that observed in the northern United States where seasonal changes are greater (Chart 3). During the course of their studies on experimental syphilis, Brown, Pearce and Van Allen[5b] observed a seasonal variation in the organ and gland weights of normal rabbits. Certain of

these variations assumed a seasonal cycle similar to those just mentioned, while almost exactly reversed or reciprocal curves were obtained in the weights of other glands.

Brown and Pearce[45] demonstrated experimentally that seasonal variations in the susceptibility of rabbits to experimental syphilis can be accounted for by variations in the degree of exposure to light. Pearce and Brown[26] showed a similar effect of light on the susceptibility of rabbits to a transplantable neoplasm. The observation by Kligler and Weitzman[17] that increased exposure to light increases the susceptibility of guinea-pigs to trypanosome infection provides an example of the same seasonal factor (light) affecting the animal economy in such a way that opposite effects are brought about on host resistance in two species—increased resistance to *T. pallida* in rabbits and increased susceptibility to trypanosomes in guinea-pigs.

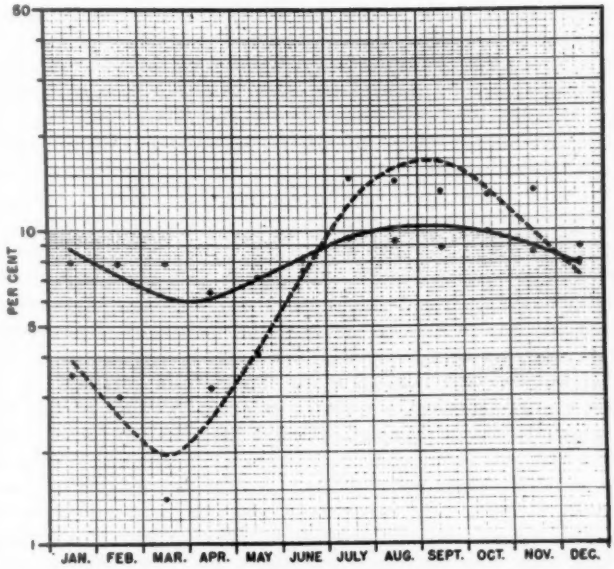

CHART 3.—Seasonal variation in iodine content of thyroid gland in cattle in the United States and sheep in England. Sheep ———; cattle — — —. (Reprinted from J. Prev. Med., **3**, 245, 1929.)

Arnold and Brody[1] found that exposure to high temperature and humidity depressed the normal gastro-duodenal bactericidal action in the dog, permitting an increased passage of bacteria from the stomach and duodenum to the cecum. In repeated observations from which it must be concluded that seasonal fluctuations in the efficiency of normal defense mechanisms do occur, Wilson[42] and Pritchett[28] observed similar seasonal fluctuations in the mortalities resulting from experimental mouse typhoid, which under the conditions of the experiment can best be explained by seasonal variation in host resistance. Moragues and Pinkerton[23] reported that mice of the same stock strain showed widely different mortality rates following injection with the rickettsia of typhus fever when kept at different temperatures—the higher temperatures rendering the mice more susceptible. Colvin and Mills[6] pointed out that mice adapted to life in a

moist, high temperature are more susceptible to infection than those adapted to life in cooler environments.

These studies, as well as those of Südmersen and Glenny[36] with diphtheria toxin and of Hunt[14] with acetonitrile, suggest that the physiologic variations brought about by seasonal and environmental changes may be closely related to differences in host receptivity which, in turn, may be one factor determining the seasonal pattern of disease. The significance of these studies lies in the fact that they indicate that the host is not in a state of physiologic stability, but, rather, undergoes seasonal changes of a character similar to the seasonal periodicity of disease. Such variations can hardly be considered as abnormal or pathologic, but as normal adjustments of the host to variations in its environment. As Hunt[14] said, ". . . . man is doubtless daily producing profound effects upon his resistance to poisons and diseases . . . ." The relationship between such physiologic variation and susceptibility to disease perhaps lies in a failure of such adjustment in some respect, resulting in a physiologic imbalance.

That the frequency with which infection results in clinical disease or immunity without disease in the human host may be determined by factors residing entirely within the host seems well established in diphtheria. The Negro race enjoys a comparative freedom from clinical diphtheria despite ample evidence that infection and immunization take place as readily as in the white race.[2a] Studies in familial susceptibility to poliomyelitis,[2g] leprosy,[2d] tuberculosis,[29] diabetes[2g,16] and rheumatic fever[43] have indicated that the major determinant of disease often is within the host. Experimentally, the studies of Webster[40c] on mice and of Lurie[19] on rabbits have clearly established that susceptibility to a given infectious agent may be determined by host factors. Indeed, in experimental bacteriology, the selection of the proper strain of experimental animal has become a laboratory commonplace.

The observation that clinical disease results in but few of the many exposed to the same infectious agent is good indication that the receptivity of the host is determined in part at least by factors other than acquired or induced immunity. Paralytic poliomyelitis occurs in few of those infected with the virus—indeed clinical disease, either paralytic or non-paralytic, is relatively infrequent when it is remembered that exposure to the virus is almost universal. The incidence of bulbar poliomyelitis following tonsillectomy provides a good example of an induced autarceologic change precipitating disease in a virus carrier.[2h] The pneumococcus carrier, too, has been observed to suddenly develop pneumonia for reasons not yet clearly defined, due to the same type of organism he has harbored for some time.

Susceptibility, as measured by the Dick test, is generally taken to indicate susceptibility to scarlet fever. However, it has been repeatedly shown among school children attending the same grade in the same school that a Dick positive may harbor the identical strain of hemolytic streptococcus producing scarlet fever in the child at the next desk, and will develop either a mild "sore throat" or no clinical illness at all; the Dick test in such case often remaining positive.[37] Furthermore, a known toxigenic strain may attain the same degree of dispersion in two groups of similar age and immunity status, and will produce disease in one group while remaining innocuous in the other group.[9] Such observations suggest the existence of factors other than susceptibility to erythrogenic toxin which determine in part whether or not clinical infection follows exposure. Rheumatic fever, a serious sequel to streptococcal infection, is precipi-

tated in relatively few of the many infected at some time or other with the hemolytic streptococcus. The same is true of meningococcus meningitis. A comparison of the carrier rate for Type 1 meningococcus with the incidence of clinical disease makes it clear that a very small percentage of those who harbor the organism develop meningitis.

There is some evidence that differences in host resistance are determined by physiologic as well as genetic differences. Among these physiologic variations, differences in the economy of the endocrine hormones may be one factor which influences the reaction of the host to a given infectious agent.[2b] As is well known, pregnancy affects the development or progress of several diseases. These effects may be the net result of mechanical or nutritional stress, or may be the result of some intrinsic physiologic factor associated with the utilization of the sex hormones. Pregnancy may be a predisposing factor in lethargic encephalitis[20] and poliomyelitis.[2f] On the other hand, there is no adequate explanation for some of the effects noted—the "therapeutic" effect of pregnancy on syphilis,[35] or the resistance of pregnant and lactating animals to experimental syphilitic infection.[4a] Experimental studies indicate that the estrogenic substances exert a protective effect against the intranasal instillation of poliomyelitis virus in monkeys,[2d] and against pneumococcal[39a] and streptococcal[7] infection in mice, while the opposite—an enhancement of the disease process—has been observed in experimental tuberculosis in guinea-pigs.[37]

There is evidence of significant changes in the condition of the nasopharynx, a common portal of entry for infection, brought about by changes in temperature and humidity, which may well be related to host resistance. Hill and Muecke[12] showed that the nasal mucosa remains swollen and edematous for some time following exposure to a warm, moist atmosphere. Mudd *et al.*[25] found that body chilling is associated with a marked drop in the temperature of the nasal and postnasal cavities.

As long ago as 1896, Malling-Hansen[22] observed seasonal variations in weight increase in children—the greatest weight increase occurring from August to the middle of September, and the least during early spring and summer. Vahl[38] found that female children gained weight faster in summer than winter, while Porter[27] observed that the weight gained by male children in the first and last 5 months of the year was in the ratio of 1 to 4.1.

Aycock[2a] found that in Massachusetts the average number of cases of poliomyelitis occurring in the first 5 months of the year was 1 to 4.2 to those occurring during the last 5 months of the year. In Chart 4 the average percentage gain in weight each month (Porter's study) is compared with the seasonal distribution of poliomyelitis.

That seasonal physiologic differences do exert a definite influence on the seasonal prevalence of disease is emphasized by the fact that susceptibility to certain non-infectious diseases (where the factors of "seasonal transmission" and "microbic variation" need not be considered) exhibit characteristic seasonal variations, *e. g.*, pellagra. Rickets furnishes another example of the influence of physiologic variation on seasonal fluctuation. Hess and Lundagen[11a] found a seasonal variation in the blood phosphate of infants which corresponds closely with the seasonal variation of healing rickets, as described by Schmorl.[30]

Reciprocal Seasonal Prevalence. In general, seasonal curves which are different in shape even though they may reach their peaks at the same season are suggestive of the operation of different and unrelated mechan-

isms. Where 2 diseases have seasonal curves which are either identical with or exactly the reverse of each other, the operation of the same influence on the 2 diseases, either in the same or in the opposite manner is suggested.

As already pointed out, the season of prevalence of epidemic typhus fever (European) is the reverse of that of other insect-borne diseases as a group. Furthermore, the shape of the seasonal curve of louse-borne typhus is not only different but almost the exact reciprocal of that of flea-borne American typhus (Chart 5). Ample evidence affords the explanation, of course, that the two forms of the disease have reversed seasonal curves, not because of different and unrelated mechanisms of spread, but because the 2 insect vectors thrive under opposite seasonal influences.

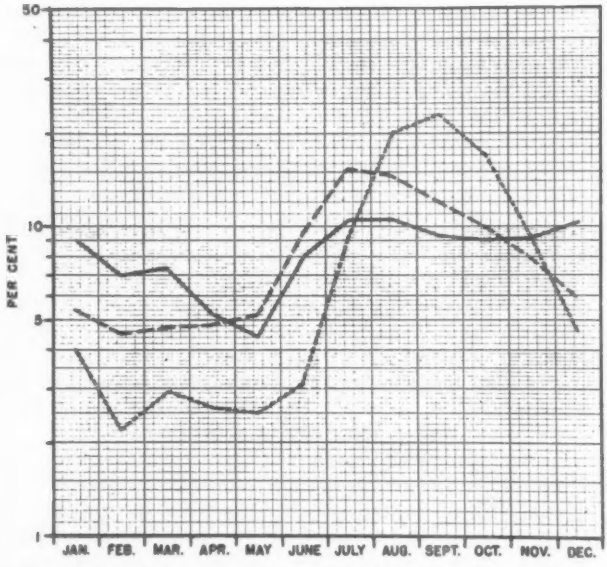

CHART 4.—Seasonal variation in average percentile gain in weight in school children as compared with seasonal fluctuation in poliomyelitis. Poliomyelitis: Massachusetts – – – – – –; Southern — — —. Rate of growth ———. (Reprinted from J. Prev. Med., **3**, 245, 1929.)

Thus, typhus fever furnishes an example of the same principle of transmission producing reversed seasonal curves due to opposite effects of the same influence (season) on 2 different vectors—the 1 being favored in the same order as the other is inhibited by season.

A classical experimental example of reciprocal seasonal effects of the same mechanism is seen in the work of Reid Hunt[14] many years ago, wherein it was shown that the seasonal curves of toxicity of acetonitrile for mice and for guinea-pigs were almost exactly the opposite (Chart 5).

Most of the ordinary poisons undergo no marked chemical changes in the body before exerting their toxic effects. Acetonitrile, however, is poisonous only, or largely as a result of the formation from it of hydrocyanic acid, according to Hunt. The formation of hydrocyanic acid is due to certain processes of metabolism which are seasonal and may be modified by factors which influence metabolism as, for example, diet or

the administration of thyroid. Numerous experiments showed that minute amounts of thyroid fed to rats and guinea-pigs increased susceptibility of these animals to acetonitrile. The opposite effect—increased resistance to this poison, is produced when thyroid is fed to mice.

Hunt suggests as an explanation of this seemingly paradoxical reaction that in mice acetonitrile tends to be changed to acetamid and that in mice thyroid increases this reaction rather than the formation of hydrocyanic acid, the reaction which is increased by the administration of thyroid to rats or guinea-pigs. Hunt's suggestion is based on the fact that acetamid has the same odor as that which is peculiar to mice, although it has never been shown that the characteristic odor of mice is actually due to the presence of this substance.

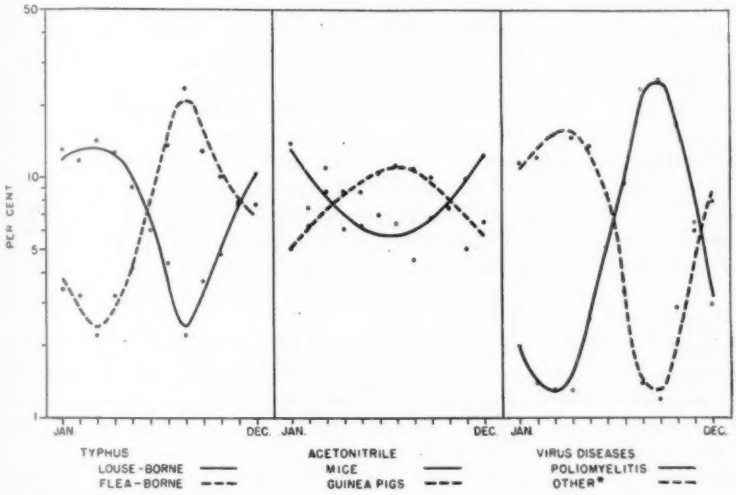

CHART 5.—Reciprocal seasonal curves, in the same virus disease, in the toxicity of the same poison, and in virus diseases in the same host, as determined by reversed activity of different vectors, different hosts, and different virus. (Data from League of Nations Bull., 1929–1934; Hyg. Lab. Bull., No. 33, 1907; No. 69, 1910.)

Thus the acetonitrile phenomenon affords an example of the opposite seasonal effect of the same toxic agent—administered in the same way in 2 animals. Here the reciprocal seasonal effect is clearly due to the fact that the 2 different experimental animals possess different faculties of metabolizing the acetonitrile—the one in the direction of toxicity and the other in the opposite direction. Since seasonal variation in metabolic processes are the same in the 2 animals, the result is a reversal of seasonal curves of toxicity in the 2 experimental animals.

If the acetonitrile be likened to virus and its administration to mode of spread, the acetonitrile phenomenon becomes a good analogy in the epidemiologic sense to the same virus transmitted in the same way producing reciprocal curves of seasonal prevalence in 2 different hosts. And it may be commented here that if the seasonal curves in the 2 animals were the only data presented, it would hardly be inferred by the process of reasoning ordinarily used in epidemiology in interpreting seasonal prevalence, that the 2 animals had been "infected with" the same "causative agent" in the same way.

The modes of spread of practically all infectious diseases are no longer in question. In some, a single basic observation or experiment has been sufficient to settle any question of mode of spread. In others, the mode of spread is clearly indicated by the general features of distribution of the disease. In still others, modes of spread are readily accepted not so much because of anything which can be called proof in the usual sense of the word, but because of similarities in distribution to other diseases in which "proof" has been elicited in one way or another. As already pointed out, seasonal prevalence has been a favorite basis for inference as to modes of spread, and to many, the character of its curve has been enough to stamp a disease as having a given mode of spread.

Poliomyelitis is unique amongst the infectious diseases in that its mode of spread has remained a subject of heated controversy. The classic studies of Caverly, Wickman, Frost, Flexner and Lewis and many others all afford evidence of transmission by ordinary human contact. The evidence in favor of this concept of the epidemiology of poliomyelitis is easily of the order of that readily accepted as conclusive proof in many other diseases. And yet it has been subjected to innumerable checks and challenges. The basis of these objections has always lain in the well-known and constantly reiterated fact that the seasonal prevalence of poliomyelitis is the opposite of that of the contact diseases as a group. A number of studies have grown out of this single objection, the results of which are, to be sure, consistent in themselves with other modes of spread. These have been stressed as indicating other modes of spread, in spite of the fact that similar objections to accepted modes of spread in other diseases can be equally well supported.

A similar challenge to accepted modes of spread in many other infectious diseases doubtless would elicit findings equally inconsistent in themselves with accepted modes of spread. Poliomyelitis not only reaches its peak of prevalence in the opposite season from that of a number of the upper respiratory infections, but, as in the 2 examples cited, typhus fever and acetonitrile, its seasonal curve is the reciprocal of that of the composite seasonal curve of a number of upper respiratory virus infections (Chart 5). The fact that the seasonal curve of poliomyelitis is the exact reciprocal of that of the upper respiratory group, not merely "reaching its peak in the opposite season," is enough to suggest that it is not due to the operation of a different and unrelated mode of spread, but to the operation in reversed order of the same mechanism which determines the seasonal curve of the group of upper respiratory diseases in general.

It might also be remarked here that the fact that there is a seasonal curve which is the reciprocal of that of the winter upper respiratory group of virus infections might be taken in itself as an indication that the winter-prevalent virus infections are not the direct result of crowding. If it were, its reciprocal curve would suggest the effect of the opposite of crowding—population dispersal—and one cannot conceive of dispersal of population in itself favoring any mode of spread.

Thus in typhus fever, louse-borne or epidemic and flea-borne or endemic; in the acetonitrile phenomenon, in mice and rats or guinea-pigs; and in the seasonal phenomenon of poliomyelitis and the group of upper respiratory virus infections, there are 3 examples of reciprocal seasonal prevalence. In typhus it is clear that the reversed seasonal curves are due not to different mechanisms of spread but, rather, to reversed bionomics of the 2 insect vectors. In the acetonitrile phenomenon it is likewise clear that reversed seasonal curves are due to reversed effects of the

same seasonal factor on the conversion of the non-toxic acetonitrile into a toxic substance in the 2 host animals.

In view of the weight of evidence to the effect that the virus of poliomyelitis is transmitted by person-to-person contact, the proposition is made that its seasonal curve is similarly due to the operation in the reversed order of the same factor which is responsible for the seasonal fluctuation in upper respiratory virus infections as a group.

These 3 examples of reversed seasonal prevalence in what can be termed the same mechanism of spread, serve to illustrate the complex nature of parasite—environment—host relationships in epidemiology as well as to emphasize the fact that seasonal prevalence is not a criterion for mode of spread alone, but may reflect seasonal variation in parasites themselves, in environmental factors affecting their transmission, or in the susceptibility or reaction of the host to the disease agent.

Summary. "Si nous reprenons maintenant l'examen du problème que soulève la régularité si grande de la plupart de nos maladies épidémiques, une question se pose tout d'abord; ce phénomène est-il du au microbe ou à l'individu atteint?"[21]

A hypothesis early advanced and now become a legend as the preferred explanation of the genesis of epidemics is "increase in virulence of the infective agent by rapid passage." Since in most infections transmitted directly from human to human, "epidemics" are in reality seasonal increases in prevalence, this explanation becomes at the same time the commonly accepted explanation for seasonal prevalence.

The sole basis for the idea of increased virulence as the responsible factor in epidemics is the stepping up in virulence with rapid passage when an infectious agent is first transferred to an experimental animal. There is actually no evidence that this is a reflection of what happens in the natural host, or that increase in virulence in the experimental animal constitutes an increase in virulence for the natural host. On the contrary, there are many indications that it represents a process of adaptation of the organism to an unaccustomed host.

Reasons have been given which indicate that seasonal prevalence in the upper respiratory diseases is not simple seasonal variation in opportunities of transmission of the infectious agents according to the older generalization, but, rather, a far more complex seasonal variation in the parasite—host interaction.

There is no clear-cut evidence that parasites themselves undergo seasonal changes in virulence. Although the *frequency* of disease varies greatly with season, in some cases in the face of uniform prevalence of the infective agent, there is no corresponding variation either in the severity of clinical manifestations or in case fatality rate, as might be expected if the infective agent were undergoing seasonal changes in its pathogenicity. In other words, the character of the disease produced is the same whether it is occurring rapidly and in large numbers, or slowly and in small numbers.

On the other hand, we see many seasonal variations in physiologic activity which are in general considered as normal changes which take place concomitantly with seasonal changes in the environment in which we live. None the less many of these seasonal undulations are of the same character of seasonal fluctuations in disease—non-infectious and infectious. Furthermore, examples have been given particularly in the experimental field where certain of these normal seasonal variations in physiology can be associated with variations in resistance to fixed toxic agents. It is not meant to imply here that seasonal variations in physiology are in them-

selves pathologic. They undoubtedly are normal, adaptive adjustments to the changing environment. It would rather appear that any association with susceptibility to infection resides in faults or failures in seasonal changes in physiology.

As judged from the magnitude of seasonal variations in infectious disease, in harborage of certain infectious agents and in physiologic functions, it is anticipated that the host-parasite interaction may be affected by season in 2 distinct ways. Seasonal changes in the host may have the simple effect of producing a seasonal variation in resistance to disease while not necessarily affecting the harborage or transmission of the infectious agent. On the other hand, both resistance to disease and resistance to infection (multiplication of the virus which in turn affects transmission) may be influenced by season.

Differences in the magnitude of seasonal variation in a number of infectious diseases affords some indication that the former may be a general rule in bacterial infections, and the latter in virus infections—a point, however, which will require further investigation.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF JANUARY 16, 1945

Hematological Changes Produced by Large Doses of Atabrine. CHARLES W. MUSHETT and HENRY SIEGEL (Merck Institute for Therapeutic Research, Rahway, N. J.). The oral administration of large doses of atabrine to rats, mice, rabbits, hamsters, guinea-pigs, dogs, monkeys, chickens and ducks resulted in definite hematologic changes. These consisted of anemia, leukocytosis, the appearance of peculiar basophilic inclusions in the cytoplasm of lymphocytes and in erythrocytes and alterations in the differential count. The appearance of lymphocytic inclusions after atabrine therapy was a constant feature in all species, while the other changes varied with the species. With Romanowsky stains, such as Wright's solution, the lymphocytic inclusions appeared as dark blue staining bodies in the cytoplasm varying in size and shape from minute punctate granules to large irregularly shaped masses. These bodies were so large they often caused bulging of the lymphocytes and were frequently associated with increased vacuolization. Inclusions of a similar nature, but smaller in size were irregularly distributed in erythrocytes, particularly in cells with a polychromatophilic staining reaction. While lymphocytic inclusions were seen in all 9 species used, erythrocytic inclusions were observed only in rats, mice and hamsters. Anemia was observed in the rat, monkey and dog. Leukocytosis was noted in the rat and leukopenia in the rabbit, dog and monkey. The differential change usually consisted of a lymphopenia and polynucleosis, while the rat showed, in addition, a monocytosis. It is considered unlikely that the blood changes might be due to the activation of a latent infection, such as that caused by Bartonella or a related organism. It must be emphasized that the dose of atabrine which produces blood changes in laboratory animals is considerably larger than that ordinarily used for the treatment of malaria in humans.

Reduced Acute Toxicity of Antigens in Saline-in-Oil Emulsion. SEYMOUR P. HALBERT, JOSEPH SMOLENS and STUART MUDD (Department of Bacteriology, University of Pennsylvania). The degree of reduction of the acute toxicity of various antigens in a saline-in-mineral-oil emulsion has been investigated. The lethal toxicities for mice by the subcutaneous route of the antigens diluted in saline were compared with those of the same antigens prepared as saline-in-mineral-oil emulsions. In most cases, 50% survival doses were determined. The quantitative estimations of the fold decreases of the materials studied are: *S. paradysenteriæ* Flexner

V368 antigen, 9 fold; Shiga neurotoxin, 20 fold; Botulinus toxin, 43 fold; Ricin (a plant toxin), 49 fold; tetanus toxin, 100 fold, 326 fold (two experiments).

Other reports have indicated that the oil-emulsion technique improves antigenicity. The above results would seem to indicate that this menstruum offers promise for the reduction of acute toxicity as well.

The Behavior of Inhaled Particles in Different States of Aerosol Suspension as Indicated by Pulmonary Tuberculosis in Rabbits. W. F. WELLS and H. L. RATCLIFFE (Laboratories for the Study of Air-borne Infection and Department of Pathology, School of Medicine, University of Pennsylvania). Settling velocity is probably the most important physical characteristic of air-borne particles. It integrates the elementary features of size, density and shape, upon which depend the pollution and purification of air. Since air drag, weighed by settling velocity, carries particulate matter into the respiratory tract, particles of different settling velocity are likely to result in different disease patterns from air-borne infection.

Several years ago, an apparatus for the simultaneous exposure of rabbits up to the number of 6 to inhalation of quantitative doses of air-borne infection was exhibited to the Society. Last year procedures for the suspension of particles of uniform size and the determination of their settling velocity were described. Wells and Lurie had previously shown that tubercle bacilli in nuclei settling less than one-tenth of a foot per minute were almost quantitatively inhaled into the lung of rabbits, and in 4 weeks these developed into discrete tubercles which could be readily counted. The tubercle bacillus therefore appears to be a suitable tracer organism for the quantitative determination of the deposition of inhaled particles in the alveoli.

Experiments have since been conducted using improved apparatus and techniques by which particles of uniform settling velocity may be inhaled. The number of tubercles produced by inhalation of particles settling a foot a minute has been compared with the number produced by approximately the same number of infected nuclei settling less than a tenth of a foot a minute. In these experiments broth cultures of the Ravenel strain were grown in revolving Erlenmeyer flasks with beads. The process breaks up the growing mass of organisms, so a filtrate through a No. 4 Whatman filter shows a majority of the organisms to be in single form which can be counted by the Breed method. Equal quantities of this suspension were added to a 1% and a 40% solution of Difco brain-heart medium and atomized into the air which the rabbits breathed for 30 minutes.

In 1 experiment 4 rabbits exposed to the small nuclei settling less than a tenth of a foot a minute gave, after 4 weeks, 1 negative, 2 with single tubercles in the lung, and 1 with 2 tubercles in the lung. Four rabbits exposed to nuclei settling a foot per minute showed no tubercles after 7 weeks. In a second experiment using larger numbers in the aerosol, 5 rabbits breathing the smaller nuclei gave 22, 16, 21, 26 and 17 tubercles at the end of 4 weeks. Four rabbits breathing the larger nuclei gave 4, 3, 3 and 5 tubercles in the lung. In a third experiment 6 rabbits inhaling somewhat larger nuclei showed 5, 6, 4, 13, 20 and 15 tubercles at the end of 30 days. All 5 similar rabbits breathing the smaller nuclei showed more than 100 tubercles each in the same time. No evidence of infection of other organs in the body was found. The fate of the organisms which did not reach the lung has not yet been ascertained.

In view of the fact that nuclei from body fluids coughed or sneezed into the atmosphere may be of the dimensions of the smaller nuclei, while particles of dust raised from dried sputum would probably be coarser than the large nuclei, these experiments would seem to be significant in a study of air-borne infection. Most of the bacteria-bearing particles observed in normal inhabited atmospheres are of the order of magnitude of the larger nuclei and the coarser fragments from infected clothing or bedding would probably be even greater. There may be a difference in the mode of infection of the nose and throat, by organisms such as streptococci or diphtheria bacilli in infected dust and the so-called contagious virus infections which spread dynamically through aggregations sharing confined atmospheres.

Osmotic and Ionic Equilibria Between the Erythrocyte and a Complex External Solution. M. H. JACOBS and DOROTHY R. STEWART (Department of Physiology, University of Pennsylvania). The nature of the osmotic and ionic equilibria between a normal erythrocyte, permeable to all anions and no cations, and its normal surrounding medium, the plasma, has been discussed in detail by Van Slyke, Wu, and McLean. In experimental work with drugs which are weak bases it is necessary in addition to consider penetrating molecules and what in effect are penetrating cations. Other situations may arise which involve non-penetrating anions and non-electrolytes. All possible cases of this sort, numbering several hundred, may be dealt with together by considering the most complex case possible, namely, that in which penetrating and non-penetrating anions, cations, and molecules, respectively, and proteins are all present in the external medium. The problem involves the determination of 6 unknowns, *i. e.*, the internal pH of the cell, the degree of ionization of its hemoglobin, its water content and the distribution ratios for penetrating anions, cations and molecules, respectively. To find these 6 unknowns, 6 relations among them are available, which, when properly combined, lead to a relatively simple solution. Appropriate equations for the simpler particular cases that arise in practice are obtained by substituting in the general solution the value zero for all the missing quantities. Four such equations when applied to the distribution of salts of weak bases explain in part the low distribution ratios reported for such substances in the case of the erythrocyte, the inapplicability of Nernst's distribution law, the swelling of the erythrocyte in the presence of ammonium salts, and other observed facts. An application of these principles gives a method for the detectionof ammonium salts in concentrations at least as low as 0.00003 M.

Changes in the Non-protein Fractions of the Plasma Nitrogen Following Extensive Thermal Burns.* JAMES WALKER, JR. (Pennsylvania Hospital and Harrison Dept. of Surgical Research, Univ. of Penna.). In a study of the toxemia syndrome in over 100 thermal burns, detailed analyses of the non-protein nitrogen fractions of the plasma nitrogen were carried out in 18 patients. It was observed that the severity of the clinical picture seemed to be closely correlated with the elevation of the plasma non-protein nitrogen and that all of the patients in the larger series in whom the non-protein nitrogen rose to above 100 mg. per 100 ml. of plasma died. Urea nitrogen, uric acid nitrogen, creatinine nitrogen and alpha amino nitrogen were analyzed separately and seldom increased very much.

* Work done under contract with the Office of Scientific Research and Development.

Fifty to 80% of the rise occurred in the undetermined fraction of the non-protein nitrogen. The level of this undetermined fraction rose rapidly and progressively in most of the fatal cases. In non-fatal cases in which the clinical picture of toxemia developed it rose for a time and then fell irregularly.

In fatal cases there was autopsy evidence of severe injury to the kidney tubules but in spite of this, nitrogen output was gradually increased in the urine and fractionation of urinary non-protein nitrogen revealed that 30 to 50% of the increase was in the undetermined fraction.

Whether any of this undetermined nitrogen represents a toxic factor or whether it is merely a response to tissue injury remains uncertain.

XUM

BOOK REVIEWS AND NOTICES

A TEXTBOOK OF PATHOLOGY. Pathologic Anatomy in Its Relation to the Causes, Pathogenesis, and Clinical Manifestations of Disease. By ROBERT ALLAN MOORE, Edward Mallinckrodt Professor of Pathology, Washington University School of Medicine, St. Louis. Pp. 1338; 513 figs.; 34 in color. Philadelphia and London: W. B. Saunders, 1944. Price, $10.00.

THIS new textbook replaces in the Saunders' list that classic, McCallum's Textbook of Pathology, which recently has been discontinued with the death of Dr. McCallum. This is obviously a tough assignment. Despite this psychologic handicap, the book gets off to a good start and will undoubtedly be a strong competitor in its field.

The organization of the book is unusual, being a compromise between the conventional pattern of general, followed by systemic, or special, pathology and the modern attempt to arrange on an etiologic basis. The major division into general and special pathology is conventional, with sections arranged from various points of view.

In the general pathology section, degenerations are divided into disturbances of protein, carbohydrate, lipid, and mineral metabolism, rather than the more usual descriptive anatomic approach. On the whole this is a distinct improvement. However, it does have the disadvantage of implying more precise knowledge of many of these obscure processes than is accepted by most pathologists. A separate chapter on the disturbances of body fluids is a welcome innovation in pathology texts.

Following the general pathology section is a group of chapters dealing with various types of infections. These have been classified on the basis of the portal of entry. Thus, chapters are given over to such portals as the skin, respiratory, alimentary, and genital tracts. This classification leaves a large group of miscellaneous infections, other bacteria, rickettsia, viruses, fungi, and parasites, to be taken up in separate chapters.

Major subdivisions are then given to diseases caused by physical agents, chemicals, pregnancy and the newborn, and deficiencies.

The last half of the book is a review of diseases of unknown cause. Those of each system and organ are taken up in separate chapters, in the conventional systemic method of special pathology.

The text "reads" easily and is well documented, especially as regards summarizing articles. The illustrations are excellent, a high percentage being actual photographs, many in color, with many good drawings from McCallum's book. The book is well printed on excellent paper, exceptional in these war days.

All agree that an "etiological classification" of disease is a desirable ideal. When infectious diseases are to be discussed such a method is a necessity. However, in a textbook of pathology such a small part of the lesions discussed fall readily into this group that it seems doubtful whether the orderly systemic classification should be upset more than is necessary in order that this special group may receive the best treatment. It is the Reviewer's opinion that none of the new classifications, either Dr. Moore's or those of other standard texts, have any advantage over the old conventional systemic classification.

Dr. Moore has made full use of the "etiological classification." This makes for excellent organization in some portions, but is clumsy and inconvenient when the same organism, streptococcus, let us say, produces important lesions with different disease pictures in various parts of the body. Other innovations seem of doubtful value, especially that of classifying diseases by portal of entry. Also when considering diseases of an organ, it is disconcerting and often

inconvenient to have to look in many widely separated chapters for the various types of lesions. It seems to the Reviewer that the resulting incoördination is too high a price to pay for the partial attainment of an "etiological classification."

On the whole, however, Dr. Moore has done an excellent job. As a student textbook, this book should undoubtedly take its place as an equal with other standard works. Pathologists will find it of value for quick reference and its bibliographies of value for locating summary articles. It can be recommended for both student and specialist. W. S.

ENDOCRINOLOGY OF WOMAN. By E. C. HAMBLEN, B.S., M.D., F.A.C.S., Clinical Professor of Endocrinology and Associate Professor of Obstetrics and Gynecology, Duke University School of Medicine; Chief of the Endocrine Division and Endocrinologist, Duke Hospital, Durham, N. C. Pp. 571; 157 figs. Springfield, Ill.: Charles C Thomas, 1945. Price, $8.00.

THE first half of the book deals with the anatomy and the normal and applied physiology of all the endocrine organs, and diagnostic methods. The second half treats of endocrine diseases, with special emphasis on gynecologic conditions. The text is designed for practical clinical usefulness, and it is systematically and concisely written. Although there are two chapters on the thyroid, no mention is made of non-toxic nodular goiter. Numerous illustrations are from the author's material and reproductions of charts and tables from publications by others. Many references are given at the bottom of the pages and at the end of the chapters.

The Reviewer protests, on the grounds of moral principles, against the author's advocating masturbation to obtain seminal fluid. The author's opposition to the use of androgens in women is to be commended. The Reviewer dislikes the author's insistence that the mother shall not be present during the vaginal examination of her child, and deplores a number of other expressions of his point of view. I. Z.

MEDICAL USES OF SOAP. Edited by MORRIS FISHBEIN, M.D. With 10 Authors. Pp. 182; 41 figs. Philadelphia: J. B. Lippincott, 1945. Price, $3.00.

ALTHOUGH scattered articles, a number by some of the present authors, have appeared in the literature on soap, this book represents a complete symposium on the medical uses of soap. Between two covers one can obtain authoritative answers to the questions usually asked by patient and physician alike about soap, detergents, and similar subjects.

This book should rightfully be called *Soap, a Medical Problem.*

The range of material includes: (1) Soap Technology; this is a discussion of the chemistry and manufacture of soap, a presentation of the new detergents, and the mechanism of detergency or cleansing action. (Daniel J. Kooyman and G. Thomas Halberstadt.) (2) Usual or Normal Effects of Soap on the "Normal" Skin. (3) Unusual or Abnormal Effects of Soap on the "Normal" Skin. (4) The Effects of Soap on the Abnormal or Diseased Skin. (Marion B. Sulzberger and Rudolf L. Baer.) (5) The Effects of Soap on the Hair. (Theodore Cornbleet.) (6) Soaps for Industry and the Industrial Worker. (Carey McCord.) (7) Soap for Shaving. (Lester Hollander.) (8) Cutaneous Detergents Other than Soap. (C. Guy Lane and Irvin H. Blank.) (9) The Medical Uses of Soap. (Morris Fishbein.)

A fine production, this book is worthy of the consideration of all physicians especially general practitioners, industrial physicians, and dermatologists. It is a good reference book for anyone, medical or lay, who is interested in soap. H. B.

XUM

METASTASES. Medical and Surgical. By MALFORD W. THEWLIS, M.D., Attending Specialist in General Medicine, U.S.P.H. Hospitals, New York City; Attending Physician, South County Hospital, Wakefield, R. I.; Special Consultant, Rhode Island Dept. Public Health; Author, Care of the Aged (Geriatrics), Preclinical Medicine. Foreword by HUBERT A. ROYSTER, A.B., M.D., F.A.C.S., Honorary Chief Surgical Service, Rex Hospital; Chief-of-Staff, St. Agnes Hospital; Consulting Surgeon, Dix Hill State Hospital; Fellow, American Board of Surgery, Raleigh. Pp. 230; 13 ills. Charlotte, N. C.: Charlotte Medical Press, 1944. Price, $5.00.

IT is unbelievable that this volume could be offered in good faith as "helpful to students, to general practitioners, to busy surgeons or to roentgenologists who want to refresh their memories." From Foreword to finish this book represents the most ridiculous jumble of nonsense and errors that the Reviewer has encountered in modern medical literature. An excerpt from the Foreword states that "Even if the 'cause of metastasis is not known' ready recognition of its possibilities will save lives. Study of this volume will contribute effectively to that result." The author's Preface informs us that "This book is an outline of medical and surgical metastases, merely an adjunct to three-dimensional anatomy and pathology." The scope and arrangement of the volume is described by the author as follows: "General considerations are *given* in Section I; in Section II neoplasms are *considered;* in Section III infections are *recorded;* in Section IV infectious diseases are *noted;* in Section V miscellaneous diseases are *taken up;* and in Section VI regional areas are *discussed.* [Editor's italics.]

"The following references in the text are given: A, type or site of primary lesion; B, source of metastases; C, location of metastases."

The section on General Considerations commences with the following illuminating discussion of the term metastasis: "Metastasis is defined as 'the transfer of a disease process from a primary focus to a distant one by the conveyance of the causal agents through blood vessels or lymph vessels.' The term metastasis may be applied to 'movement of bacteria from one part of the body to another; or a change in location of a disease or of its manifestations or transfer from one organ to another.' It also applies to the 'subsidence of an inflammation that at the same time appears in another part' (Taber). The prefix meta is used to denote change of place, order, condition or nature; stasis is stagnation or stoppage of the circulation of any fluids of the body."

The text of Sections II to VI consists of list of primary sites and locations of metastases. For example (pp. 33–34): "Adamantinoma: A. Hypophysis; Jaw, especially lower jaw; Lung; Lymph-nodes; Nasopharynx; Orbit; Pituitary gland; Tibia. [No B—ED.] C. Rarely metastasizes. Slow growth. To: Glands, cervical; Lung; Ovary; Tibia." [The author's tabular arrangement of this and the following quotation has been altered to save space.—ED.] Why hypophysis and pituitary gland are listed separately is not clear. It is also rather disconcerting to learn that adamantinomas arise in so many localities. Also perplexing is to discover that bronchogenic cancer metastasizes to osteoarthropathy (p. 37) and that fibrocarcoma (presumably fibrosarcoma) does not often metastasize (p. 40). One more example taken from the section on neoplasms (pp. 51–52) will suffice): "Schuller-Christian Syndrome (Exanthomatosis): A. Bone; Skin, especially of eyelids. C. To: Ascites; Bone (defects in skull and long bones); Brain; Diabetes insipidus; Exophthalmos; Joints; Liver; Lungs; Lymphnodes (regional); Lymph nodes; Perinephric suppuration; Perinephritis without suppuration; Peritoneum; Pleura; Ribs; Spleen."

Enough? Or must I include sickle-cell anemia metastasizing to fat embolism (p. 83) and biliary cirrhosis metastasizing to osteoarthropathy (p. 85) to convince the reader of this review that he had better spend his $5.00 on War stamps? One wonders whether the author and his publisher are aware of the paper shortage in this country. D. C.

ADVANCES IN PROTEIN CHEMISTRY. VOLUME I. Edited by M. L. ANSON, Continental Foods, Hoboken; JOHN T. EDSALL, Harvard Medical School; and 9 Contributors. Vol. 1. Pp. 341; numerous figs. and tables. New York: Academic Press, Inc., 1944. Price, $5.50.

THIS is the first volume of a projected series dealing with advances in various fields of protein chemistry. Eight contributors discuss proteins as they occur in complex biologic systems of nature—fields that have been neglected in many of the recent monographs on proteins.

The range of topics discussed is indicated by the titles of the chapters: Lipoproteins (E. Chargaff), Structural Proteins of Cells and Tissues (F. O. Schmitt), Some Contributions of Immunology to the Study of Proteins (H. P. Treffers), The Interaction Between Alkali Earth Cations, Particularly Calcium, and Proteins (D. M. Greenberg), The Purification and Properties of Certain Protein Hormones (B. F. Chow), Soybean Protein in Human Nutrition (D. S. Payne and L. S. Stuart), Nucleoproteins (J. P. Greenstein), and The Proteins of Skeletal Muscle (K. Bailey).

The authors have been very successful in presenting a survey of knowledge within these special fields, and are to be congratulated upon the excellency of their products. With the increase in interest in the rôle of proteins and amino acids in the physiologic economy of the body this volume should find a wide audience. H. V.

VITAMINS AND HORMONES. Advances in Research and Applications. Edited by ROBERT S. HARRIS, Associate Professor of Nutritional Biochemistry, Massachusetts Institute of Technology, and KENNETH V. THIMANN, Associate Professor of Plant Physiology, Harvard University. Vol. 2. Pp. 514; numerous figs. and tables. New York: Academic Press, 1944. Price, $6.80.

THE editors have maintained the high standard of choice of topics and contributors that was evident in Volume 1 of this series of Reviews. The subjects covered, and the authors are as follows: (1) The Role of Vitamins in the Anabolism of Fats, by E. W. McHenry and M. L. Cornett; (2) The Chemistry of Biotin, by D. B. Melville; (3) The Nutritional Requirements of Primates other than Man, by P. L. Day; (4) Physiological Action of Vitamin E and Its Homologues, by K. E. Mason; (5) The Chemistry and Physiology of Vitamin A, by I. M. Heilbron, W. E. Jones, and A. L. Bacharach; (6) Para-Aminobenzoic Acid—Experimental and Clinical Studies, by S. Ansbacher; (7) A Critique of the Etiology of Dental Caries, by G. J. Cox; (8) Vitamins and Cancer, by D. Burk and R. J. Winzler; (9) Effect of Androgens and Estrogens on Birds, by A. S. Parkes, and C. W. Emmens; (10) Hormones in Cancer, by E. C. Dodds; (11) *X*-ray Crystallography and Sterol Structure, by D. Crowfoot.

These critical reviews and condensations of the literature, by recognized leaders, should find a welcome place in the libraries of investigators interested in Nutrition and Physiology. H. V.

SURGICAL DISORDERS OF THE CHEST. Diagnosis and Treatment. By J. K. DONALDSON, B.S., M.D., F.A.C.S., MAJOR, M.C., A.U.S.; Diplomate, American Board of Surgery; Associate Professor of Surgery and in charge of Thoracic Surgery, University of Arkansas School of Medicine, etc., Surgical Staff, St. Vincent's Infirmary and Visiting Staff, Baptist Hospital, Little Rock, Ark.; Formerly Chest Surgeon to Arkansas State Hospital for Nervous Diseases; Associate Surgeon, Robert B. Green Hospital, Visiting Surgeon to Santa Rosa, Nix, and Medical Arts Hospital, San Antonio, Texas. Pp. 364; 127 figs. Philadelphia: Lea & Febiger, 1944. Price, $6.50.

THIS is a thoroughly practical volume presenting a comprehensive survey of the rapidly advancing field of thoracic surgery with its many ramifications. The author has recognized the need of general practitioners and general surgeons, as well as students and residents, for an epitomized volume dealing with fundamental advances in this field, many of which have not as yet

appeared in book form. The volume is roughly divided into 3 parts. The first comprises an excellent section on chest injuries and their management. The second section deals with intrathoracic infections, tumors and congenital abnormalities. Included in this portion of the work are chapters on the surgery of various cardiac disorders, and the problem of pulmonary embolism. The last section deals with the surgery of pulmonary tuberculosis. The text is written critically. The bibliography is ample and the illustrations well chosen and numerous. In the Reviewer's opinion it is a very much worthwhile book.

L. S.

HEART DISEASE. By PAUL DUDLEY WHITE, M.D., Lecturer in Medicine, Harvard Medical School; Physician to the Massachusetts General Hospital, Boston. Third Ed. Pp. 1025; 138 ills. New York: Macmillan, 1944. Price, $9.00.

THIS 3rd edition is illustrative of the author's characteristic care in the thorough way in which he has revised an already excellent book to keep it up to date in a constantly advancing subject. And then to leave no stone unturned, he adds an addendum of chapter by chapter additions "inadvertently neglected." His new chapter on the range of the normal heart will be useful to all, and especially valuable to those who tend to set up rigid normal figures for a normality that spreads over wide ranges. Many a figure that is normal for one may be clearly abnormal for another individual. A pleasant and useful feature that could well be imitated in other American textbooks is the inclusion of perspective-giving historical sidelights and an appendix of cardiac chronology (omitted from the 2nd edition).

Dr. White's long-held authoritative position in American cardiology is further enhanced by this clearly written, well-presented, well-illustrated volume.

E. K.

NEW BOOKS

Colloid Chemistry. Theoretical and Applied. By SELECTED INTERNATIONAL CONTRIBUTORS. Collected and Edited by JEROME ALEXANDER. Vol. 5. Theory and Methods, Biology and Medicine. Pp. 1256; numerous figs. and tables. New York: Reinhold, 1944. Price, $20.00.

Photoelements and Their Application. By DR. BRUNO LANGE, Consulting Engineer, Berlin-Dahlem, Formerly Research Physicist with Kaiser Wilhelm Institute, Berlin. Translated by ANCEL ST. JOHN, PH.D., New York. Pp. 297; 67 figs. New York: Reinhold, 1938. Price, $10.00.

Medico-legal Blood Group Determination. Theory, Technique, Practice. By DAVID HARLEY, M.D., B.Sc., F.I.C., The Laboratories of the Inoculation Department, St. Mary's Hosp., London. Second Impression. Pp. 119; 13 figs. New York: Grune & Stratton, 1944. Price, $3.50.

The Amino Acid Composition of Proteins and Foods. Analytical Methods and Results. By RICHARD J. BLOCK, PH.D., Associate in the Department of Physiology and Biochemistry, New York Med. Coll.; Research Director, C. M. Armstrong, Inc., New York City; Formerly Research Associate in Chemistry, New York State Psychiatric Institute and Hosp., New York City; Consultant in the Chemistry of Proteins and Amino Acids; and DIANA BOLLING, B.S. Pp. 396. Springfield, Ill.: Thomas, 1945. Price, $6.50.

The Photochemistry of Gases. By WILLIAM ALBERT NOYES, JR., Professor of Chemistry, Univ. of Rochester, and PHILIP ALBERT LEIGHTON, Professor of Chemistry, Stanford Univ. Pp. 475; 66 figs. New York: Reinhold, 1941. Price, $10.00.

Arterial Hypertension. Its Diagnosis and Treatment. By IRVINE H. PAGE, M.D., and ARTHUR CURTIS CORCORAN, M.D., Research Division of the Cleveland Clinic Foundation, Cleveland; Formerly Lilly Laboratory for Clinical Research, Indianapolis City Hospital, Indianapolis. Pp. 352; numerous figs. Chicago: Year Book Publishers, 1945. Price, $3.75.

XUM

Shoulder Lesions. By H. F. Moseley, M.A., D.M., M.Ch. (Oxon.), F.R.C.S. (Eng. and C.), F.A.C.S., Montreal, Canada; Lecturer in Surgery, McGill Univ.; Assistant Surgeon, Royal Victoria Hosp. Pp. 181; 70 figs. Springfield, Ill.: Thomas, 1945. Price, $4.50.

NEW EDITIONS

Internal Medicine. Its Theory and Practice. In Contributions by American Authors. Edited by John H. Musser, B.S., M.D., F.A.C.P., Professor of Medicine in the Tulane Univ. of Louisiana School of Medicine; Senior Visiting Physician to the Charity Hosp., New Orleans, La. Fourth Ed. Pp. 1518; numerous figs. Philadelphia: Lea & Febiger, 1945. Price, $10.00.

Fischerisms. Being a sheaf of sundry and divers utterances culled from the lectures of Martin H. Fischer, Professor of Physiology in the Univ. of Cincinnati. By Howard Fabing. This 3rd Edition by Ray Marr. Pp. 83. Springfield, Ill.: Thomas, 1944. This volume is a private print for his students.

"Fourteen years have elapsed since the first edition of Fischerisms. Many students who had the privilege of sitting at your feet these past years, have wanted but could not obtain the volume. In this time new aphorisms were jotted down upon our notebooks, many more upon the tablet of our memory."

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